caspase-3-like activity [redacted] not required for either caspa[redacted]2 processing or apoptosis in this paradigm. An **antisense** oligonucleotide to caspase-2 inhibited cell death but did not affect caspase-3-like activity, indicating that caspase-2 is not upstream of this activity and that activation of caspase-3-like caspases is not sufficient for death. Thus, in our paradigm, caspase-2 processing and caspase-3-like activity are induced independently of each other. Moreover, although death requires caspase-2, caspase-3-like activity is neither necessary nor sufficient for death.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09713560 98451107
Evidence of a direct role for **Bcl-2** in the regulation of articular chondrocyte apoptosis under the conditions of serum withdrawal and retinoic acid treatment.
Feng L; Precht P; Balakir R; Horton WE Jr
Laboratory of Biological Chemistry, Gerontology Research Center, National Institute on Aging, NIH, Baltimore, Maryland 21224, USA.
Journal of cellular biochemistry (UNITED STATES) Nov 1 **1998**, 71 (2) p302-9, ISSN 0730-2312 Journal Code: HNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The regulation of chondrocyte apoptosis in articular cartilage may underlay age-associated changes in cartilage and the development of osteoarthritis. Here we demonstrate the importance of **Bcl-2** in regulating articular chondrocyte apoptosis in response to both serum withdrawal and retinoic acid treatment. Both stimuli induced apoptosis of primary human articular chondrocytes and a rat chondrocyte cell line as evidenced by the formation of DNA ladders. Apoptosis was accompanied by decreased expression of aggrecan, a chondrocyte specific matrix protein. The expression of **Bcl-2** was downregulated by both agents based on Northern and Western analysis, while the level of Bax expression remained unchanged compared to control cells. The importance of **Bcl-2** in regulating chondrocyte apoptosis was confirmed by creating cell lines overexpressing sense and **antisense Bcl-2** mRNA. Multiple cell lines expressing **antisense Bcl-2** displayed increased apoptosis even in the presence of 10% serum as compared to wild-type cells. In contrast, chondrocytes overexpressing **Bcl-2** were resistant to apoptosis induced by both serum withdrawal and retinoic acid treatment. Finally, the expression of **Bcl-2** did not block the decreased aggrecan expression in IRC cells treated with retinoic acid. We conclude that **Bcl-2** plays an important role in the maintenance of articular chondrocyte survival and that retinoic acid inhibits aggrecan expression independent of the apoptotic process.

3/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09681854 98435878
Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells.
Jee SH; Shen SC; Tseng CR; Chiu HC; Kuo ML
Department of Dermatology, College of Medicine, National Taiwan University, Taipei.
Journal of investigative dermatology (UNITED STATES) Oct **1998**, 111 (4) p656-61, ISSN 0022-202X Journal Code: IHZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Curcumin, a potent antioxidant and chemopreventive agent, has recently been found to be capable of inducing apoptosis in human hepatoma and

leukemia cells by way of an elusive mechanism. Here, we demonstrate that curcumin also induces apoptosis in human basal cell carcinoma cells in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic change. In our study, consistent with the occurrence of DNA fragmentation, nuclear p53 protein initially increased at 12 h and peaked at 48 h after curcumin treatment. Prior treatment of cells with cycloheximide or actinomycin D abolished the p53 increase and apoptosis induced by curcumin, suggesting that either de novo p53 protein synthesis or some proteins synthesis for stabilization of p53 is required for apoptosis. In electrophoretic mobility gel-shift assays, nuclear extracts of cells treated with curcumin displayed distinct patterns of binding between p53 and its consensus binding site. Supportive of these findings, p53 downstream targets, including p21(CIP1/WAF1) and Gadd45, could be induced to localize on the nucleus by curcumin with similar p53 kinetics. Moreover, we immunoprecipitated extracts from basal cell carcinoma cells with different anti-p53 antibodies, which are known to be specific for wild-type or mutant p53 protein. The results reveal that basal cell carcinoma cells contain exclusively wild-type p53; however, curcumin treatment did not interfere with cell cycling. Similarly, the apoptosis suppressor **Bcl-2** and promoter Bax were not changed with the curcumin treatment. Finally, treatment of cells with p53 **antisense** oligonucleotide could effectively prevent curcumin-induced intracellular p53 protein increase and apoptosis, but sense p53 oligonucleotide could not. Thus, our data suggest that the p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. This evidence also suggests that curcumin may be a potent agent for skin cancer prevention or therapy.

3/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09675576 98357648
Natural resistance to intracellular parasites: a study by two-dimensional gel electrophoresis coupled with multivariate analysis.
Kovarova H; Radzioch D; Hajduch M; Sirova M; Blaha V; Macela A; Stulik J; Hernychova L
Purkyne Military Medical Academy, Hradec Kralove, Czech Republic. kovarova@pmfhk.cz
Electrophoresis (GERMANY) Jun **1998**, 19 (8-9) p1325-31, ISSN 0173-0835 Journal Code: ELE
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Natural resistance to Mycobacterium bovis bacillus Calmette-Guerin (BCG) is determined by the Bcg gene (Nramp1), which is exclusively expressed by mature macrophages. The Nramp1 gene is a dominant autosomal gene that has two allelic forms; r confers resistance and s confers susceptibility to infection with intracellular pathogen. Although the wide range of pleiotropic immunological effects of the Nramp1 gene has been described, the exact mechanism of its action remains elusive. In this study we searched for differentially expressed proteins that might provide clues in the studies on Nramp1 gene function. We performed two-dimensional gel electrophoresis of cellular proteins prepared from a B10R macrophage line derived from mice carrying the r allele of the Nramp1 gene, B10S macrophages carrying the s allele, and B10R-Rb macrophages transfected with Nramp1-**ribozyme**. The classification of protein patterns and selection of distinct proteins characteristic of r or s allele-carrying macrophages was performed using the principal component analysis. We found differential expression of four proteins with the following isoelectric point/molecular weight (pI/Mr) in B10R macrophages compared to B10S and B10R-Rb macrophages: 6.6/25, 7.0/22, 9.1/31.5, and 5.3/8.5. The protein 7.0/22 has been identified as Mn-superoxide dismutase and the best candidate for protein p6.6/25 seems to be **Bcl-2** according to the immunoblot analysis. When the splenic macrophages carrying the r or s allele were

analyzed, the changes in relative abundance for proteins [redacted]/25 and p7.0/22 were satisfactorily reproduced. Overall, the two identified proteins are important in the regulation of intracellular redox balance and the regulation of apoptosis in macrophages, respectively. Our findings may suggest their possible biological role in the innate immunity against intracellular pathogens.

3/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09670786 98414428
Antisense inhibition of Bax mRNA increases survival of terminally differentiated HL60 cells.
Manfredini R; Capobianco ML; Trevisan F; Rauzi F; Barbieri D; Citro G; Tagliafico E; Ferrari S
Dipartimento di Scienze Biomediche, Sezione di Chimica Biologica, Universita di Modena, Italy.
Antisense & nucleic acid drug development (UNITED STATES) Aug **1998**, 8 (4) p341-50, ISSN 1087-2906 Journal Code: CJY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cell sensitivity to programmed cell death is primarily modulated by members of the **Bcl-2** family, as the balance of homodimer or heterodimer formation between proapoptotic and antiapoptotic members defines apoptosis susceptibility in the great majority of cellular contexts. It is, therefore, important to clarify if the Bax protein is limiting for activation of the genetic program of programmed cell death or can be complemented by different **Bcl-2** family members, such as Bak or Bad. To gain some insight into the role of Bax in the molecular mechanisms of apoptosis of myeloid cells, we inhibited this gene in all-trans-retinoic acid (ATRA)-treated HL60 cells using the methodology of **antisense** oligodeoxynucleotides (AS-ODN). Our results indicate that Bax inhibition has no effect on the proliferation and differentiation capacity of HL60 cells. Instead, the survival rate of terminally differentiated Bax-inactivated HL60 (Bax(-) HL60) cells is almost three times higher in respect to control cultures, indicating that in mature granulocytes Bax is not efficiently complemented by others members of the **Bcl-2** family proteins.

3/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09664228 99006633
Synergistic cytotoxicity of **bcl-2** **antisense** oligodeoxynucleotides and etoposide, doxorubicin and cisplatin on small-cell lung cancer cell lines.
Zangemeister-Wittke U; Schenker T; Luedke GH; Stahel RA
Department of Internal Medicine, University Hospital Zurich, Switzerland.
British journal of cancer (SCOTLAND) Oct **1998**, 78 (8) p1035-42, ISSN 0007-0920 Journal Code: AV4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Expression of **Bcl-2** is life-sustaining for small-cell lung cancer cells and associated with drug resistance. In the present study, the interactions between the **bcl-2** **antisense** oligodeoxynucleotide 2009 and the chemotherapeutic agents etoposide, doxorubicin and cisplatin were investigated on small-cell lung cancer cell lines to search for synergistic combinations. The cell lines NCI-H69, SW2 and NCI-H82 express high, intermediate-high and low basal levels of **Bcl-2** , respectively, which are inversely correlated with the sensitivities of the cell lines to treatment with oligodeoxynucleotide 2009

and the chemotherapeutic agents alone. Moreover, differences were found in the responsiveness of the cell lines to treatment with combinations of oligodeoxynucleotide 2009 and the chemotherapeutic agents. In the cell lines NCI-H69 and SW2, all combinations resulted in synergistic cytotoxicity. In NCI-H69 cells, maximum synergy with a combination index of 0.2 was achieved with the combination of oligodeoxynucleotide 2009 and etoposide. In SW2 cells, the combination of oligodeoxynucleotide 2009 and doxorubicin was the most effective (combination index = 0.5). In the cell line NCI-H82, which expresses a low basal level of **Bcl-2**, most of the combinations were slightly antagonistic. Our data suggest the use of oligodeoxynucleotide 2009 in combination with chemotherapy for the treatment of small-cell lung cancer that overexpresses **Bcl-2**.

3/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09638117 98377769
Apoptotic induction in transformed follicular lymphoma cells by **Bcl-2** downregulation.
Tormo M; Tari AM; McDonnell TJ; Cabanillas F; Garcia-Conde J; Lopez-Berestein G
Department of Bioimmunotherapy, The University of Texas M. D. Anderson Cancer Center, Houston, USA.
Leukemia & lymphoma (SWITZERLAND) Jul **1998**, 30 (3-4) p367-79, ISSN 1042-8194 Journal Code: BNQ
Contract/Grant No.: CA62597, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The roles of **Bcl-2** protein and the protein ratio of **Bcl-2** /Bax in regulating cell growth in various lymphoma cell lines were examined. A dose-dependent decrease in **Bcl-2** protein expression was observed in the different lymphomas incubated with lipid-incorporated **bcl-2 antisense** oligonucleotides (L-**bcl-2**). Growth inhibition was observed in a transformed follicular lymphoma (FL) cell line, which has the t(14;18) translocation and **Bcl-2** protein overexpression. One of the mechanisms by which L-**bcl-2** growth inhibition is mediated in these transformed FL cells might be through apoptotic induction, because the treated cells had an increased apoptotic index and showed the typical DNA fragmentation. These studies indicate that **Bcl-2** protein is critical in the growth regulation of transformed FL cells. L-**bcl-2** did not induce growth inhibition in lymphoma cells not expressing **Bcl-2** or Bax protein. Thus, the protein ratio of **Bcl-2**/Bax may also be important in regulating the growth of these lymphomas.

3/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09631309 98424844
[At the front line of malignant melanoma, great maneuvers: to cut the road to Bcl2 and "attack with chemotherapy" (news)]
Sur le front des melanomes malins, grandes manoeuvres: couper la voie a Bcl2 et "chimiotheraper".
Benard J
Bulletin du cancer (FRANCE) Jun **1998**, 85 (6) p520-1, ISSN 0007-4551 Journal Code: BDZ
Languages: FRENCH
Document type: NEWS

3/3,AB/24 (Item 24 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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09594139 98384236
Antisense to the epstein-barr virus (EBV)-encoded latent membrane protein 1 (LMP-1) suppresses LMP-1 and **bcl-2** expression and promotes apoptosis in EBV-immortalized B cells.
Kenney JL; Guinness ME; Curiel T; Lacy J
Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA.
Blood (UNITED STATES) Sep 1 **1998**, 92 (5) p1721-7, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA 67396, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The Epstein-Barr virus (EBV)-encoded latent membrane protein (LMP-1) is required for viral transformation and functions to protect cells from apoptotic cell death, in part, by induction of antiapoptotic genes, including **Bcl-2** and A20. We have used **antisense** oligodeoxynucleotides targeted to LMP-1 as a strategy to suppress LMP-1 expression and thereby inhibit its functions. We have shown that levels of LMP-1 protein in EBV-positive lymphoblastoid cell lines can be reduced by in vitro treatment with unmodified oligodeoxynucleotides targeted to the first five codons of the LMP-1 open-reading frame. Furthermore, suppression of LMP-1 was associated with molecular and phenotypic effects that included downregulation of the LMP-1-inducible antiapoptotic genes, **Bcl-2** and Mcl-1, inhibition of proliferation, stimulation of apoptosis, and enhancement of sensitivity to the chemotherapeutic agent, etoposide. These effects were largely sequence-specific and observed in EBV-positive, but not EBV-negative cell lines. These studies suggest that lowering expression of LMP-1 in EBV-associated malignancy might have therapeutic effects and might synergize with other antitumor agents. Copyright 1998 by The American Society of Hematology.

3/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09584304 98336293
mcl-1 is an immediate-early gene activated by the granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling pathway and is one component of the GM-CSF viability response.
Chao JR; Wang JM; Lee SF; Peng HW; Lin YH; Chou CH; Li JC; Huang HM; Chou CK; Kuo ML; Yen JJ; Yang-Yen HF
Institute of Molecular Biology, National Taiwan University Medical School, Taipei, Taiwan.
Molecular and cellular biology (UNITED STATES) Aug **1998**, 18 (8) p4883-98, ISSN 0270-7306 Journal Code: NGY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
mcl-1, a **bcl-2** family member, was originally identified as an early gene induced during differentiation of ML-1 myeloid leukemia cells. In the present study, we demonstrate that Mcl-1 is tightly regulated by the granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling pathway. Upon deprivation of survival factor from TF-1 myeloid progenitor cells, Mcl-1 levels quickly dropped prior to visible detection of apoptosis of these cells. Upon restimulation of these deprived cells with GM-CSF, the mcl-1 mRNA was immediately induced and its protein product was accordingly resynthesized. Analysis with Ba/F3 cells expressing various truncation mutants of the GM-CSF receptor revealed that the membrane distal region between amino acids 573 and 755 of the receptor beta chain was required for mcl-1 induction. Transient-transfection assays with luciferase reporter genes driven by various regions of the mcl-1 promoter demonstrated that the upstream sequence between -197 and -69 is responsible for cytokine

activation of the mcl-[redacted]ene. Overexpression of mcl-1 d[redacted]yed but did not completely prevent apoptosis of cells triggered by cytokine withdrawal. Its down regulation by **antisense** constructs overcame, at least partially, the survival activity of GM-CSF and induced the apoptosis of TF-1 cells. Taken together, these results suggest that mcl-1 is an immediate-early gene activated by the cytokine receptor signaling pathway and is one component of the GM-CSF viability response.

3/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09584294 98336278
Molecular determinants of AHPN (CD437)-induced growth arrest and apoptosis in human lung cancer cell lines.
Li Y; Lin B; Agadir A; Liu R; Dawson MI; Reed JC; Fontana JA; Bost F; Hobbs PD; Zheng Y; Chen GQ; Shroot B; Mercola D; Zhang XK
The Burnham Institute, Cancer Research Center, La Jolla, California 92037, USA.
Molecular and cellular biology (UNITED STATES) Aug **1998**, 18 (8) p4719-31, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: CA51933, CA, NCI; CA60988, CA, NCI; CA63783, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN or CD437), originally identified as a retinoic acid receptor gamma-selective retinoid, was previously shown to induce growth inhibition and apoptosis in human breast cancer cells. In this study, we investigated the role of AHPN/CD437 and its mechanism of action in human lung cancer cell lines. Our results demonstrated that AHPN/CD437 effectively inhibited lung cancer cell growth by inducing G0/G1 arrest and apoptosis, a process that is accompanied by rapid induction of c-Jun, nur77, and p21(WAF1/CIP1). In addition, we found that expression of p53 and **Bcl-2** was differentially regulated by AHPN/CD437 in different lung cancer cell lines and may play a role in regulating AHPN/CD437-induced apoptotic process. On constitutive expression of the c-JunAla(63,73) protein, a dominant-negative inhibitor of c-Jun, in A549 cells, nur77 expression and apoptosis induction by AHPN/CD437 were impaired, whereas p21(WAF1/CIP1) induction and G0/G1 arrest were not affected. Furthermore, overexpression of **antisense** nur77 RNA in A549 and H460 lung cancer cell lines largely inhibited AHPN/CD437-induced apoptosis. Thus, expression of c-Jun and nur77 plays a critical role in AHPN/CD437-induced apoptosis. Together, our results reveal a novel pathway for retinoid-induced apoptosis and suggest that AHPN/CD437 or analogs may have a better therapeutic efficacy against lung cancer.

3/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09583978 98294094
Need for caspase-2 in apoptosis of growth-factor-deprived PC12 cells.
Haviv R; Lindenboim L; Yuan J; Stein R
Department of Neurobiochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv University, Ramat Aviv, Israel.
Journal of neuroscience research (UNITED STATES) Jun 1 **1998**, 52 (5) p491-7, ISSN 0360-4012 Journal Code: KAC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous studies have shown that caspases (proteases related to interleukin-1beta converting enzyme) are needed for the death of trophic factor-deprived PC12 cells. However, the protease involved in this process has not been identified. The results presented here strongly suggest that

caspase-2 (Nedd2/Ich-1) plays a major role in the death of serum-deprived PC12 cells. We show that in PC12 cells overexpression of caspase-2 induces cell death, serum deprivation induces processing (i.e., activation) of the 48-kDa pro-caspase-2, and stable expression of caspase-2 **antisense** RNA inhibits apoptosis induced by serum deprivation. In addition, overexpression of **bcl-2** , which prevents this death process, also inhibits the processing of pro-caspase-2, suggesting that **bcl-2** acts upstream of pro-caspase-2 activation.

3/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09580163 98345301
Role for Bcl-xL in delayed eosinophil apoptosis mediated by granulocyte-macrophage colony-stimulating factor and interleukin-5.
Dibbert B; Daigle I; Braun D; Schranz C; Weber M; Blaser K; Zangemeister-Wittke U; Akbar AN; Simon HU
Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
Blood (UNITED STATES) Aug 1 **1998**, 92 (3) p778-83, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Eosinophils are potent inflammatory cells involved in allergic reactions. Inhibition of apoptosis of purified eosinophils by certain cytokines has been previously shown to be an important mechanism causing tissue eosinophilia. To elucidate the role of **Bcl-2** family members in the inhibition of eosinophil apoptosis, we examined the expression of the known anti-apoptotic genes **Bcl-2**, Bcl-xL, and A1, as well as Bax and Bcl-xS, which promote apoptosis in other systems. We show herein that freshly isolated human eosinophils express significant amounts of Bcl-xL and Bax, but only little or no **Bcl-2**, Bcl-xS, or A1. As assessed by reverse transcription-polymerase chain reaction, immunoblotting, flow cytometry, and immunocytochemistry, we show that spontaneous eosinophil apoptosis is associated with a decrease in Bcl-xL mRNA and protein levels. In contrast, stimulation of the cells with granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-5 (IL-5) results in maintenance or upregulation of Bcl-xL mRNA and protein levels. Moreover, **Bcl-2** protein is not induced by GM-CSF or IL-5 in purified eosinophils. **Bcl-2** protein is also not expressed in tissue eosinophils as assessed by immunohistochemistry using two different eosinophilic tissue models. Furthermore, Bcl-xL **antisense** but not scrambled phosphorothioate oligodeoxynucleotides can partially block the cytokine-mediated rescue of apoptotic death in these cells. These data suggest that Bcl-xL acts as an anti-apoptotic molecule in eosinophils. Copyright 1998 by The American Society of Hematology.

3/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09554575 98325348
Bax inhibitor-1, a mammalian apoptosis suppressor identified by functional screening in yeast.
Xu Q; Reed JC
Burnham Institute Program on Apoptosis and Cell Death Research La Jolla, California 92037, USA.
Molecular cell (UNITED STATES) Feb **1998**, 1 (3) p337-46, ISSN 1097-2765 Journal Code: C5E
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The mammalian proapoptotic protein Bax confers a lethal phenotype when expressed in yeast. By exploiting this phenotype, we have identified a novel human Bax inhibitor, BI-1. BI-1 is an evolutionarily conserved integral membrane protein containing multiple membrane-spanning segments and is predominantly localized to intracellular membranes, similar to **Bcl-2** family proteins. Moreover, BI-1 can interact with **Bcl-2** and Bcl-XL but Bax or Bak, as demonstrated by in vivo cross-linking and coimmunoprecipitation studies. When overexpressed in mammalian cells, BI-1 suppressed apoptosis included by Bax, etoposide, staurosporine, and growth factor deprivation, but not by Fas (CD95). Conversely, BI-1 **antisense** induced apoptosis. BI-1 thus represents a new type of regulator of cell death pathways controlled by **Bcl-2** and Bax.

3/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09528215 98301293
Arginine butyrate downregulates p210 bcr-abl expression and induces apoptosis in chronic myelogenous leukemia cells.
Urbano A; Koc Y; Foss FM
Section of Hematology-Oncology and Biomolecular Medicine, Evans Research Foundation, Boston University Medical Center, MA, USA.
Leukemia (ENGLAND) Jun **1998**, 12 (6) p930-6, ISSN 0887-6924 Journal Code: LEU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Downregulation of bcr-abl expression in the chronic myelogenous leukemia cell line K562 using **antisense** oligonucleotides has been shown to enhance the sensitivity of the cells to apoptotic stimuli, suggesting that p210 bcr-abl, like **bcl-2** functions as an anti-apoptosis factor (McGahon A et al, Blood 1994, 83: 1179). In these experiments, the inhibition of p210 bcr-abl expression alone was not sufficient to induce apoptosis. We demonstrated that exposure to low doses (0.5 mM) of a butyric acid analog, arginine butyrate, was capable of inducing apoptosis in selected leukemia cell lines, including K562 cells, and in fresh leukemia cells from patients with chronic myelogenous leukemia. To further explore the mechanisms of this effect, we examined expression of p210 bcr-abl after butyrate exposure and found a dose-related inhibition of p210 bcr-abl protein without concordant change in other phosphoproteins, including the JAK-1 kinase. Further analysis revealed that the inhibition of bcr-abl expression occurs due to transcriptional regulation of the bcr-abl gene by arginine butyrate. These results suggest that arginine butyrate and other butyrate analogs alone or in combination may be useful in the therapy of patients with chronic myelogenous leukemia or bcr-abl expressing acute leukemias.

3/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09518599 98281027
Bcl-2 mRNA-targeted **ribozymes**: effects on programmed cell death in chronic myelogenous leukemia cell lines.
Scheid S; Heinzinger M; Waller CF; Lange W
Department of Hematology/Oncology, University Medical Center Freiburg, Germany.
Annals of hematology (GERMANY) Mar-Apr **1998**, 76 (3-4) p117-25, ISSN 0939-5555 Journal Code: A2P
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We used synthetic RNA transcripts to prove the cleavage capability of

ribozymes targeted against **bcl-2** -related RNAs. No [redacted] cleavage occurred when control oligonucliotides were [redacted]. To assess the functional role of the specific **ribozymes** in chronic myelogenous leukemia (CML) cell lines we cultured K562, BV173, and Daudi cells for 48 h after lipofection with 10 microM oligonucleotide. An increase in apoptotic cells, dependent on **ribozyme** specificity, was shown in BV173 cells.This finding was underlined by the typical morphological changes, but there is no correlation with regard to the level of **bcl-2** protein expressed. Though **bcl-2** appears to interfere with cell death in myeloid cells, **bcl-2**-targeted **ribozymes** do not induce programmed cell death (PCD) by reducing **bcl-2** protein levels, but rather by a presently unknown mechanism.

3/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09495227 98211344
Antisense c-myc retroviral vector suppresses established human prostate cancer.
Steiner MS; Anthony CT; Lu Y; Holt JT
Department of Urology, Vanderbilt University School of Medicine, Nashville, TN 37235, USA.
Human gene therapy (UNITED STATES) Mar 20 **1998**, 9 (5) p747-55, ISSN 1043-0342 Journal Code: A12
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Prostate cancer eventually becomes androgen resistant, resumes growth, and kills the patient. Characterization of genetic events that lead to androgen refractory prostatic neoplasia has revealed the frequent overexpression of c-myc and uncontrolled prostate cancer proliferation. A novel strategy to combat advanced prostate cancer utilized a replication incompetent retrovirus that contained the mouse mammary tumor virus (MMTV) promoter within the retroviral vector to allow transcription of **antisense** c-myc gene within target prostate tumor cells. The transduction of cultured DU145 cells by XM6:MMTV-**antisense** c-myc RNA retrovirus did not affect cell proliferation in culture, yet a single direct injection of MMTV-**antisense** c-myc viral media into established DU145 tumors in nude mice produced a 94.5% reduction in tumor size compared to tumors treated with control virus MTMV sense fos and untreated tumor by 70 days. Two animals in the **antisense** c-myc-treated group had complete regression of their tumors. Histopathological examination of the tumors revealed that MMTV-**antisense** c-myc-transduced DU145 tumors had increased tumor cell differentiation, decreased invasion, and a marked stromal response. The mechanism for the antitumor effect of MMTV-**antisense** c-myc retrovirus appears to be suppression of c-myc mRNA and protein, and decreased **bcl-2** protein. The in vivo transduction of prostate cancer cells with MMTV-**antisense** c-myc retroviruses reduced tumor growth by suppressing c-myc, resulting in the down-regulation of **bcl-2** protein. Consequently, the MMTV-**antisense** c-myc retrovirus may be useful for gene therapy against advanced, hormone-refractory prostate cancer.

3/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09483924 98240808
Loss of butyrate-induced apoptosis in human hepatoma cell lines HCC-M and HCC-T having substantial **Bcl-2** expression.
Saito H; Ebinuma H; Takahashi M; Kaneko F; Wakabayashi K; Nakamura M; Ishii H
Department of Internal Medicine, School of Medicine, Keio University,

Tokyo, Japan.
Hepatology (UNITED STATES) May **1998**, 27 (5) p1235-40, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have demonstrated that sodium butyrate induces differentiation in human hepatoma cells; however, recent studies have shown that this agent causes apoptosis in some types of cancer cells. In this study, we examined whether sodium butyrate causes apoptosis in the human hepatoma cell lines, HCC-M and HCC-T. The growth of human hepatoma cells was dose-dependently reduced by sodium butyrate. Flow cytometric analysis showed cell-cycle arrest at the G1 phase in the sodium butyrate-treated cells. Apoptotic change was never found in treated cells at concentration levels of less than 5 mmol/L. Sodium butyrate decreased p53 expression and increased p21WAF-1 expression in HCC-T and HCC-M cells having the wild-type p53 gene. Western blot analysis showed that **Bcl-2** was expressed in the HCC-T and HCC-M cells, and its expression was increased after exposure to sodium butyrate. **Antisense** oligodeoxynucleotide against **bcl-2** easily caused apoptosis. These results indicate that sodium butyrate hardly induces apoptotic change in the human hepatoma cell lines, HCC-T and HCC-M, with the increase of **Bcl-2** expression. Cell-cycle arrest in the G1 phase caused by sodium butyrate was suggested to be induced by the increase in p21WAF-1 expression, but this change did not link with the p53 increase.

3/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09475577 98209220
Antisense therapy for B cell lymphomas.
Cotter FE
Molecular Haematology Unit, Institute of Child Health, London.
Cancer surveys (UNITED STATES) **1997**, 30 p311-25, ISSN 0261-2429 Journal Code: CNG
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

3/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09470819 98215921
Cytotoxicity and apoptosis produced by cytochrome P450 2E1 in Hep G2 cells.
Chen Q; Cederbaum AI
Department of Biochemistry, Mount Sinai School of Medicine, New York 10029, USA.
Molecular pharmacology (UNITED STATES) Apr **1998**, 53 (4) p638-48, ISSN 0026-895X Journal Code: NGR
Contract/Grant No.: AA03312, AA, NIAAA; AA06610, AA, NIAAA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Two Hep G2 subclones overexpressing CYP2E1 were established with the use of transfection and limited dilution screening techniques. The Hep G2-CI2E1-43 and -47 (E47) cells (transduced Hep G2 subclones that overexpress CYP2E1) grew at a slower rate than parental Hep G2 cells or control subclones that do not express CYP2E1, but remained fully viable. When GSH synthesis was inhibited by treatment with buthionine sulfoximine, GSH levels rapidly declined in E47 cells but not control cells, which is most likely a reflection of CYP2E1-catalyzed formation of reactive oxygen species. Under these conditions of GSH depletion, cytotoxicity and apoptosis were found only with the E47 cells. Low levels of lipid

peroxidation were found in the E47 cells, which became more pronounced after GSH depletion. The antioxidants vitamin E, vitamin C, or trolox prevented the lipid peroxidation as well as the cytotoxicity and apoptosis, as did transfection with plasmid containing **antisense** CYP2E1 or overexpression of **Bcl-2**. Levels of ATP were lower in E47 cells because of damage to mitochondrial complex I. When GSH was depleted, oxygen uptake was markedly decreased with all substrates in the E47 extracts. Vitamin E completely prevented the decrease in oxygen uptake. Under conditions of CYP2E1 overexpression, two modes of CYP2E1-dependent toxicity can be observed in Hep G2 cells: a slower growth rate when cellular GSH levels are maintained and a loss of cellular viability when cellular GSH levels are depleted. Elevated lipid peroxidation plays an important role in the CYP2E1-dependent toxicity and apoptosis. This direct toxicity of overexpressed CYP2E1 may reflect the ability of this enzyme to generate reactive oxygen species even in the absence of added metabolic substrate.

3/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09443017 98184650
Bcl-2 -independent Bcr-Abl-mediated resistance to apoptosis: protection is correlated with up regulation of Bcl-xL.
Amarante-Mendes GP; McGahon AJ; Nishioka WK; Afar DE; Witte ON; Green DR
Division of Cellular Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California 92121, USA.
Oncogene (ENGLAND) Mar **1998**, 16 (11) p1383-90, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Bcr - Abl is the molecule responsible for both the transformation phenotype and the resistance to chemotherapeutic drugs found in chronic myelogenous leukemia (CML) cells. Wild-type HL-60, a transformed pro-myelocytic cell line, is very susceptible to apoptosis-inducing agents. We show here that expression of Bcr - Abl in HL-60 cells rendered them extremely resistant to apoptosis induced by a wide variety of agents. The anti-apoptotic effect of Bcr - Abl was found to be independent of the phase of the cell cycle. Treatment with **antisense** oligonucleotides directed to bcr decreased the expression of the ectopic bcr - abl and restored susceptibility to apoptosis. Double mutations affecting the autophosphorylation site and the phosphotyrosine-binding motif (FLVRES) have been previously shown to impair the transforming activity of Bcr - Abl in fibroblasts and hematopoietic cells, however HL-60 cells expressing this double mutant molecule exhibited the same level of resistance to apoptosis as those expressing the wild-type Bcr - Abl. Interestingly, wild type and mutant Bcr - Abl induced in HL-60 cells a dramatic down regulation of **Bcl-2** and increased the levels of Bcl-xL. The level of Bax did not change in response to the presence of Bcr - Abl. **Antisense** oligonucleotides targeted to bcl-x downregulated the expression of Bcl-x, and increased the susceptibility of HL-60. Bcr - Abl cells to staurosporine. Importantly, HL-60 cells overexpressing Bcl-xL showed higher expression of Bcl-xL but lower resistance to apoptosis when compared to HL-60. Bcr - Abl cells. The results described here show that Bcr - Abl is a powerful mammalian anti-apoptotic molecule and can act independently of **Bcl-2** . Bcl-xL, however, seems to participate in part in Bcr - Abl-mediated resistance to apoptosis in HL-60 cells.

3/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09441585 98165784
The binding properties and biological activities of **Bcl-2** and

Bax in cells exposed to [redacted]ptotic stimuli.
Otter I; Conus S; Ravn U; Rager M; Olivier R; Monney L; Fabbro D; Borner C
Institute of Biochemistry, University of Fribourg, Rue du Musee 5, CH-1700 Fribourg, Switzerland.
Journal of biological chemistry (UNITED STATES) Mar 13 **1998**, 273 (11) p6110-20, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The oncogene product **Bcl-2** protects cells from apoptosis whereas its homolog Bax functions to kill cells. Several binding partners of **Bcl-2** and Bax have been isolated, but none of them has yet provided clues as to exactly how **Bcl-2** and Bax work. According to one view, **Bcl-2** and Bax interact with survival and death effector molecules, respectively, and neutralize each other through heterodimerization. Alternatively, **Bcl-2** requires Bax for death protection, and additional proteins bind to the heterodimer to regulate its activity. Here we used a co-immunoprecipitation strategy to distinguish between these two possibilities. We show that the **Bcl-2**-Bax heterodimer is maintained, and no other protein associates stably in detectable amounts with **Bcl-2**, Bax, or the heterodimer in anti-**Bcl-2** and anti-Bax immunoprecipitates from normal cells and cells exposed to apoptotic stimuli. Analysis of cells expressing various levels of **Bcl-2** and Bax, however, revealed that the degree of protection against apoptosis does not correlate with the number of **Bcl-2**-Bax heterodimers but the amount of **Bcl-2** that is free of Bax. In addition, the survival activity of **Bcl-2** is unaffected when Bax expression is ablated by an **antisense** strategy. Our findings suggest that the **Bcl-2** -Bax heterodimer is a negative regulator of death protection, and that **Bcl-2** requires neither Bax nor major, stable interactions with other cellular proteins to exert its survival function. We therefore propose that **Bcl-2** acts as an enzyme (capturing substrates in a transient way), as a homodi- or multimer, or through the interaction with non-proteaceous targets (lipids, ions).

3/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09431975 98172985
Growth inhibition of DU-145 prostate cancer cells by a **Bcl-2** **antisense** oligonucleotide is enhanced by N-(2-hydroxyphenyl)all-trans retinamide.
Campbell MJ; Dawson M; Koeffler HP
Division of Hematology/Oncology, Cedars-Sinai Medical Center/UCLA School of Medicine, Los Angeles, CA 90048, USA.
British journal of cancer (SCOTLAND) Mar **1998**, 77 (5) p739-44, ISSN 0007-0920 Journal Code: AV4
Contract/Grant No.: CA43277, CA, NCI; CA42710, CA, NCI; CA70675-01, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Hormonally insensitive prostate cancer is a relatively slow-growing, but usually fatal, disease with no long-term treatment options. Transformation of normal prostate cells to a malignant phenotype often involves corruption of the apoptotic machineries. **Bcl-2** protein is one of the key inhibitors of apoptosis and is often unregulated in advanced prostate cancer. The prostate cancer cell line DU-145 was used as a model of a hormonally insensitive, advanced prostate cancer. Cell growth in liquid culture was significantly inhibited by **antisense Bcl-2** oligonucleotides compared with control sense oligonucleotides; inhibition by these oligonucleotides was significantly enhanced on combination with the synthetic retinoid N-(2-hydroxyphenyl)all-trans-retinamide (2-HPR).

Interestingly, growth [redacted]bition occurred in the absen[redacted]of apoptosis as measured using two assay techniques. We hypothesize[redacted]that in these recalcitrant cells the apoptotic pathway is compromised at several levels, and **Bcl-2** may play another role in promoting cell growth. The use of **Bcl-2** **antisense** oligonucleotides plus 2-HPR may provide a novel approach to therapy of hormone-resistant prostate cancer.

3/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09425773 98165184
Differential induction of cell death in human glioma cell lines by sodium nitroprusside.
Blackburn RV; Galoforo SS; Berns CM; Motwani NM; Corry PM; Lee YJ
Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan 48073, USA.
Cancer (UNITED STATES) Mar 15 **1998**, 82 (6) p1137-45, ISSN 0008-543X Journal Code: CLZ
Contract/Grant No.: CA 48000, CA, NCI; CA 44550, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: High grade gliomas represent very aggressive and lethal forms of human cancer, which often exhibit recurrence after surgical intervention and resistance to conventional chemotherapeutic and radiologic treatment. The clinically approved antihypertensive agent sodium nitroprusside (SNP) has been shown to induce cytotoxicity toward a number of carcinoma cell lines in vitro. METHODS: Three human glioma cell lines were examined for susceptibility to the cytotoxic effects of SNP. The role of the protein kinase C (PKC)alpha gene in mediating resistance to SNP-induced killing in U343 cells was investigated using **antisense** oligonucleotide inhibition. Stable transfection and overexpression of the PKCalpha gene in the SNP-susceptible cell line U251 was performed to further implicate PKCalpha as a mediating factor in SNP cytotoxicity. In addition, the presence of **bcl-2** protein in these cells was examined for possible correlation(s) with resistance to SNP. RESULTS: Exposure of U251 cells and LN-Z308 cells to 0.5 mM SNP resulted in significant cytotoxicity over a 72-hour period. U343 cells were resistant to SNP killing. U343 cells were shown to exhibit higher basal levels of PKCalpha and **bcl-2** than either U251 or LN-Z308 cells. **bcl-2** expression and resistance to SNP toxicity both were decreased by the introduction of PKCalpha **antisense** oligonucleotides into U343 cells. Conversely, enhanced PKC activity in PKCalpha-transfected U251 clones was associated with increased **bcl-2** expression and greater resistance to SNP-induced toxicity relative to control transfected cells. CONCLUSIONS: SNP can induce cytotoxicity in glioma cells. The susceptibility of these glioma cells to nitroprusside-induced killing appears to be correlated inversely with **bcl-2** and PKC activity. **bcl-2** levels in these cells can be altered through modulation of PKC signaling, specifically, by induction or inhibition of PKCalpha. These in vitro results provide an interesting basis for further study into the potential use of SNP for treatment of human gliomas in patients receiving combination therapy with conventional chemotherapeutic agents that exhibit PKC inhibitory activity.

3/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09420684 98119890
The HIV-1 vpr protein acts as a negative regulator of apoptosis in a human lymphoblastoid T cell line: possible implications for the pathogenesis of AIDS.

Conti L; Rainaldi G; M[redacted]rrese P; Varano B; Rivabene R; [redacted]olumba S; Sato A ; Belardelli F; Malorni [redacted]Gessani S
Laboratory of Virology, Istituto Superiore di Sanita, Viale Regina Elena, 299-00161 Rome, Italy.
Journal of experimental medicine (UNITED STATES) Feb 2 **1998**, 187 (3) p403-13, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Although apoptosis is considered one of the major mechanisms of CD4(+) T cell depletion in HIV-infected patients, the virus-infected cells somehow appear to be protected from apoptosis, which generally occurs in bystander cells. Vpr is an auxiliary HIV-1 protein, which, unlike the other regulatory gene products, is present at high copy number in virus particles. We established stable transfectants of CD4+ T Jurkat cells constitutively expressing low levels of vpr. These clones exhibited cell cycle characteristics similar to those of control-transfected cells. Treatment of control clones with apoptotic stimuli (i.e., cycloheximide/tumor necrosis factor alpha (TNF-alpha), anti-Fas antibody, or serum starvation) resulted in a massive cell death by apoptosis. In contrast, all the vpr-expressing clones showed an impressive protection from apoptosis independently of the inducer. Notably, vpr **antisense** phosphorothioate oligodeoxynucleotides render vpr-expressing cells as susceptible to apoptosis induced by cycloheximide and TNF-alpha as the control clones. Moreover, the constitutive expression of HIV-1 vpr resulted in the upregulation of **bcl-2** , an oncogene endowed with antiapoptotic activities, and in the downmodulation of bax, a proapoptotic factor of the **bcl-2** family. Altogether, these results suggest that low levels of the endogenous vpr protein can interfere with the physiological turnover of T lymphocytes at early stages of virus infection, thus facilitating HIV persistence and, subsequently, viral spread. This might explain why apoptosis mostly occurs in bystander uninfected cells in AIDS patients.

3/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09418709 98143545

1,25-Dihydroxyvitamin D3 protects human leukemic cells from tumor necrosis factor-induced apoptosis via inactivation of cytosolic phospholipase A2.

Wu YL; Jiang XR; Lillington DM; Allen PD; Newland AC; Kelsey SM
Department of Hematology, St. Bartholomew's and The Royal London School of Medicine and Dentistry, University of London, United Kingdom.
Cancer research (UNITED STATES) Feb 15 **1998**, 58 (4) p633-40, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The mechanism by which tumor necrosis factor (TNF) induces death of cancer cells appears to involve the activation of cytosolic phospholipase A2 (cPLA2). U937 human leukemic cells treated with 1,25-dihydroxyvitamin D3 [1,25(OH)2D3; 10(-8) M] become resistant to TNF, an effect that is independent of cell cycle status and expression of TNF receptors or **BCL-2** . In this study, TNF produced a dose- and time-dependent enhancement of [3H]arachidonic acid release in U937 cells. The amount of [3H]arachidonic acid release was positively associated with TNF-induced apoptosis. Both immunofluorescence microscopy and Western blotting of cell subcompartments demonstrated translocation of cPLA2 from the cytosol to the cell membrane in response to TNF. In addition, TNF up-regulated expression of cPLA2 mRNA. An **antisense** oligonucleotide to cPLA2 and the cPLA2 inhibitor 4-bromophenacyl bromide significantly inhibited TNF-induced cytotoxicity. Prior incubation of cells with 1,25(OH)2D3 significantly inhibited (a) TNF-induced [3H]arachidonic acid release and apoptosis, (b) TNF-induced translocation of cPLA2 to the membrane, and (c) the

up-regulation of cPLA2 m[redacted] with TNF. Furthermore, the in[redacted]itory effect of 1,25(OH)2D3 was not reversed by inhibitors of transcription or translation. The data suggest that activation of cPLA2 is involved in TNF-induced apoptosis of leukemic cells. 1,25(OH)2D3 directly inhibits cPLA2 translocation and mRNA up-regulation induced by TNF. Disruption of cPLA2 activation may represent a possible mechanism whereby leukemic cells can become resistant to TNF-mediated killing.

3/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09397900 98121097
bcl-2 antisense therapy chemosensitizes human melanoma in SCID mice.
Jansen B; Schlagbauer-Wadl H; Brown BD; Bryan RN; van Elsas A; Muller M; Wolff K; Eichler HG; Pehamberger H
Department of Clinical Pharmacology, University of Vienna, Austria.
Nature medicine (UNITED STATES) Feb **1998**, 4 (2) p232-4, ISSN 1078-8956 Journal Code: CG5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Malignant melanoma is a prime example of cancers that respond poorly to various treatment modalities including chemotherapy. A number of chemotherapeutic agents have been shown recently to act by inducing apoptosis, a type of cell death antagonized by the **bcl-2** gene. Human melanoma expresses **Bcl-2** in up to 90% of all cases. In the present study we demonstrate that **bcl-2 antisense** oligonucleotide treatment improves the chemosensitivity of human melanoma grown in severe combined immunodeficient (SCID) mice. Our findings suggest that reduction of **Bcl-2** in melanoma, and possibly also in a variety of other tumors, may be a novel and rational approach to improve chemosensitivity and treatment outcome.

3/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09397899 98121095
Inhibition of neointimal cell bcl-x expression induces apoptosis and regression of vascular disease.
Pollman MJ; Hall JL; Mann MJ; Zhang L; Gibbons GH
Falk Cardiovascular Research Center, Division of Cardiovascular Medicine, Stanford University, California 94305-5246, USA.
Nature medicine (UNITED STATES) Feb **1998**, 4 (2) p222-7, ISSN 1078-8956 Journal Code: CG5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We postulated that activation of a genetic program that tonically inhibits intimal cell death is a necessary condition for the pathogenesis of vascular disease. Studies of vascular lesions in humans and animal models documented increased expression of the anti-apoptotic gene product Bcl-xL within intimal cells. Downregulation of intimal cell bcl-xL expression with the use of **antisense** oligonucleotides induced apoptosis and acute regression of vascular lesions. These findings indicate that apoptosis regulatory genes such as bcl-xL are critical determinants of intimal lesion formation and that targeted apoptosis may be a novel therapy for intimal vascular disease.

3/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09381003 98082987
Epstein-Barr virus LMP1 modulates the malignant potential of gastric carcinoma cells involving apoptosis.
Sheu LF; Chen A; Wei YH; Ho KC; Cheng JY; Meng CL; Lee WH
Department of Pathology, Tri-Service General Hospital, Taipei, Taiwan, Republic of China.
American journal of pathology (UNITED STATES) Jan **1998**, 152 (1) p63-74, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
About 10% of gastric carcinomas including lymphoepithelioma-like carcinoma and adenocarcinoma are associated with Epstein-Barr virus (EBV) infection. In EBV-associated gastric carcinomas, the tumor cells express Epstein-Barr nuclear antigen 1 (EBNA-1) but not EBNA-2, -3A, -3B, or -3C, leader protein, or latent membrane proteins (LMPs) because of gene methylation. Only a few exceptional cases have LMP1 expression in tumor cells as demonstrated by immunohistochemical studies. To elucidate the biological effects of LMP1 and the significance of its restricted expression in EBV-associated gastric carcinomas, the LMP1 gene was transferred into EBV-negative gastric carcinoma cell lines (SCM1 and TMC1) and into EBV-negative nasopharyngeal carcinoma (NPC) cells (HONE-1) as a control. The biological effects of LMP1 in gastric carcinoma cells were monitored in vitro and in vivo. These results showed that the consequence of LMP1 expression is a growth enhancement in NPC cells, but it is a growth suppression in gastric carcinoma cells. The LMP1-expressing gastric carcinoma cells had a reduced growth rate, colony-forming efficiency, mean colony size, and tumorigenicity and a lower malignant cytological grade. The reduced growth rate, colony-forming efficiency, and mean colony size were partially reversible in vitro with treatment with LMP1 **antisense** oligonucleotide. In addition, enhanced apoptosis was found in the LMP1-expressing gastric carcinoma cells. This suggests that LMP1 may negatively modulate the malignant potential of gastric carcinoma cells via an enhancement of apoptosis. We concluded that the restriction of LMP1 expression in EBV-associated gastric carcinomas may lead to a growth advantage for tumor cells by avoiding LMP1 apoptotic effects and immunologically mediated elimination.

3/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09375302 98103643
c-myc **antisense** oligodeoxynucleotides enhance the efficacy of cisplatin in melanoma chemotherapy in vitro and in nude mice.
Citro G; D'Agnano I; Leonetti C; Perini R; Bucci B; Zon G; Calabretta B; Zupi G
Laboratory of Experimental Chemotherapy, Regina Elena Cancer Institute, Centro Ricerca Sperimentale, Rome, Italy.
Cancer research (UNITED STATES) Jan 15 **1998**, 58 (2) p283-9, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
This study was designed to assess the efficacy of a new antimelanoma therapeutic strategy that relies on the use of a c-myc **antisense** 15-mer phosphorothioate oligodeoxynucleotide ([S]ODN), in combination with cisplatin (cis-diamminedichloroplatinum; DDP), which is currently used in the clinical management of melanoma patients. Proliferation and colony formation of melanoma cells were both inhibited by the DDP/c-myc **antisense** [S]ODN combination to a greater extent than that observed with either agent alone. Inhibition was most effective when DDP was followed by c-myc **antisense** [S]ODNs. Cell cycle flow cytometric analysis of cells exposed to the two agents either alone or in combination demonstrated that (a) c-myc **antisense** [S]ODNs induced an accumulation

of cells in S phase and apoptosis in a fraction of the cells, detectable at day 5 after the beginning of treatment; (b) DDP induced a block in G2-M phase detectable at day 1, which was partially recovered, and apoptosis similar in extent to that induced by c-myc **antisense** [S]ODNs; and (c) DDP and c-myc **antisense** [S]ODNs together induced arrest in G2-M phase, which was maximum at day 3, i.e., delayed as compared to the block induced by DDP. The combination induced a higher percentage of apoptosis, evident at day 3 from the start of treatment, that correlated with a marked reduction in **Bcl-2** expression. Mice bearing human melanoma xenografts and treated sequentially with DDP and c-myc **antisense** [S]ODNs showed a higher inhibition of tumor growth, reduction in the number of lung metastases, and increase in life span compared with those treated with either agent alone. Together, these data lend support to the development of anticancer therapies involving oncogene-targeted **antisense** ODNs and conventional antineoplastic drugs.

3/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09365319 98074644
Development of a hammerhead **ribozyme** against **BCL-2**. II. **Ribozyme** treatment sensitizes hormone-resistant prostate cancer cells to apoptotic agents.
Dorai T; Goluboff ET; Olsson CA; Buttyan R
Department of Urology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
Anticancer research (GREECE) Sep-Oct **1997**, 17 (5A) p3307-12,
ISSN 0250-7005 Journal Code: 59L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: Several lines of evidence strongly implicate a crucial role for the apoptosis suppressing **bcl-2** oncogene in the genesis of hormone-refractory human prostate cancer. By efficiently destroying the intracellular **bcl-2** mRNA, one might be able to make the prostate cancer cell responsive again to conventional apoptotic stimuli such as androgen withdrawal. To achieve this end, we have devised a catalytic **antisense** RNA strategy (**Ribozyme**) for **bcl-2** and evaluated its gene therapeutic potential. METHODS AND RESULTS: **Bcl-2** overexpressing LNCaP prostatic carcinoma cells (LNCaP/**bcl-2**) were transfected with the anti-**bcl-2** **ribozyme** RNA using a polyamine-based transfection reagent and the reduction in the intracellular **bcl-2** mRNA levels was followed by a ribonuclease protection assay. Using a cell viability assay, prior **ribozyme** transfection and subsequent application of apoptotic stimuli such as serum starvation or phorbol ester treatment caused a 30% increase in cell death by apoptosis than with these apoptotic stimuli alone. CONCLUSIONS: The results obtained strongly support the ability of a potential anti-**bcl-2** **ribozyme** therapy to synergize with other agents in inducing apoptosis of hormone-resistant human prostate cancer cells.

3/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09351395 98065788
Induction of heat shock protein 70 protects thymocytes against radiation-induced apoptosis.
Gordon SA; Hoffman RA; Simmons RL; Ford HR
Department of Surgery, University of Pittsburgh Medical Center, Pa, USA.
Archives of surgery (UNITED STATES) Dec **1997**, 132 (12) p1277-82,
ISSN 0004-0010 Journal Code: 8IA

Contract/Grant No.: A[redacted]869, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
OBJECTIVES: To determine if induction of heat shock protein 70 (HSP 70), a stress protein that plays a cytoprotective role and inhibits cell death in response to various stimuli, will protect thymocytes and T-cell clones from radiation-induced apoptosis, and to define the mechanism of such protection. DESIGN: Thymocytes from BALB/c mice or T-lymphocyte clones were incubated at 43 degrees C for 1 hour to induce HSP 70, then irradiated. Control cells were irradiated but not heated. Fragmentation of DNA was quantitated, and p53, bax, and **bcl-2** expression was analyzed at various times by the Western blot method. RESULTS: Only heated cells expressed HSP 70. The induction of HSP 70 increased basal apoptosis but significantly decreased radiation-induced apoptosis. Furthermore, introduction of an HSP 70 **antisense** oligomer prior to heating reversed the protective effect of HSP 70. Induction of HSP 70 in T-cell clones with sodium arsenite had a similar protective effect against radiation-induced apoptosis. Irradiation induced p53 and markedly up-regulated bax. The expression of p53 peaked at 4 hours and preceded maximal bax induction. Induction of HSP 70 prior to irradiation suppressed p53 and significantly decreased bax levels. Levels of **bcl-2** were unaffected. CONCLUSIONS: Our data show that HSP 70 induction protects thymocytes from radiation-induced apoptosis by down-regulating p53 and bax expression. The induction of HSP 70 may represent a novel mechanism by which the immunosuppressive effects and the associated infectious complications of radiation therapy can be minimized.

3/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09324679 98042368
Caspase-mediated apoptosis in AK-5 tumor cells: a cell-free study using peptide inhibitors and **antisense** strategy.
Anjum R; Khar A
Centre for Cellular and Molecular Biology, Hyderabad, India.
Experimental cell research (UNITED STATES) Nov 1 **1997**, 236 (2) p371-7, ISSN 0014-4827 Journal Code: EPB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
An in vitro system has been employed to study the apoptotic mechanisms in the AK-5 tumor which is a spontaneously regressing rat histiocytoma. Cytosolic extracts of tumor cells primed for apoptosis using dexamethasone and immune serum from tumor-regressing animals were able to induce apoptosis in intact nuclei and reproduce the classical morphological and biochemical features typical of apoptotic cells. The cleavage of lamin A and PARP to signature fragments by these extracts and the inhibition of the same using peptide inhibitors signify the pivotal role of ICE and ICE-related proteases in apoptosis. Lamin A cleavage was insensitive to YVAD but PARP cleavage was blocked by both YVAD and DEVD. Cell extracts derived from cells overexpressing the **Bcl-2** gene and Nedd-2 **antisense** gene, respectively, failed to induce apoptosis in exogenously added nuclei, suggesting that **Bcl-2** gene product is downregulating a key event in apoptotic cascade. The study also demonstrates the coherent action of different ICE-related proteases in apoptosis and their functional redundancy. This system may prove useful for analyzing complex molecular mechanisms underlying apoptosis in tumor cells.

3/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09320706 98051053

A novel Bcl-x isofo[redacted] connected to the T cell [redacted]eptor regulates apoptosis in T cells.

Yang XF; Weber GF; Cantor H

Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.

Immunity (UNITED STATES) Nov **1997**, 7 (5) p629-39, ISSN 1074-7613 Journal Code: CCF

Contract/Grant No.: AI37833, AI, NIAID; AI12184, AI, NIAID; AI13600, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We define a novel Bcl-x isoform, Bcl-x gamma, that is generated by alternative splicing and characterized by a unique 47 amino acid C-terminus. Bcl-x gamma is expressed primarily in thymocytes, where it may depend on an interaction between the TCR and host MHC products, and in mature T cells, where its expression is associated with ligation of the T cell receptor. Overexpression of Bcl-x gamma in T cells inhibits activation-induced apoptosis; inhibition of Bcl-x gamma, after stable expression of Bcl-x gamma **antisense** cDNA, enhances activation-induced apoptosis. In contrast to other Bcl-x isoforms, cells that fail to express Bcl-x gamma after CD3 ligation undergo programmed cell death, while activated T cells that express Bcl-x gamma are spared. Identification of Bcl-x gamma helps provide a molecular explanation of T cell activation and death after antigen engagement.

09317592 98043628

Thrombopoietin upregulates the promoter conformation of p53 in a proliferation-independent manner coincident with a decreased expression of Bax: potential mechanisms for survival enhancing effects.

Ritchie A; Gotoh A; Gaddy J; Braun SE; Broxmeyer HE

Departments of Microbiology/Immunology, Medicine (Hematology/Oncology), and the Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN, USA.

Blood (UNITED STATES) Dec 1 **1997**, 90 (11) p4394-402, ISSN 0006-4971 Journal Code: A8G

Contract/Grant No.: R01 HL 56416, HL, NHLBI; R01 HL 54037, HL, NHLBI; P01 HL 53586, HL, NHLBI; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Thrombopoietin (Tpo) has proliferative and maturational effects on immature and more committed cells, respectively. We previously reported a role for Tpo as a survival factor in the factor-dependent human cell line M07e by demonstrating that Tpo suppresses apoptosis in the absence of induced proliferation. Wild-type p53 is a tumor suppressor gene that can play a vital role in mediating growth factor withdrawal-induced apoptosis in factor-dependent hematopoietic cells. Wild-type p53 can switch from a suppressor conformation, with an antiproliferative, pro-apoptotic phenotype, to a promoter conformation that has a diminished ability to mediate cell cycle arrest and apoptosis. In an effort to elucidate the mechanisms through which Tpo suppresses apoptosis, we investigated the effects of Tpo treatment on p53-mediated apoptosis in M07e cells. Tpo upregulated the expression of the promoter conformation of p53 in M07e cells coincident with a downregulation of Bax and Mdm2 protein levels. Protein levels of **Bcl-2** and Bcl-xL did not significantly vary as a function of growth-factor stimulation. Conversely, the levels of suppressor conformation p53 were maximal when M07e was in a growth arrested state and decreased during factor stimulation. Furthermore, Tpo treatment induced an extranuclear buildup and greatly weakened the DNA binding capacity of p53. p53-specific **antisense** oligonucleotide treatment recapitulated the effects of Tpo treatment on the levels of Bax, Mdm-2, and

Bcl-2 . These results [redacted]ggest that Tpo is suppressing [redacted]wth factor withdrawal induced-apoptosis, at least in part, by downregulating the expression of pro-apoptotic Bax protein levels, through modulating the conformation of p53, which results in a functional inactivation of its pro-apoptotic abilities.

3/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09313849 98018548
A **Bcl-2** **antisense** oligonucleotide increases alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) toxicity in cortical cultures.
White MJ; Chen J; Zhu L; Irvin S; Sinor A; DiCaprio MJ; Jin K; Greenberg DA
Department of Neurology, University of Pittsburgh School of Medicine, PA 15261, USA.
Annals of neurology (UNITED STATES) Oct **1997**, 42 (4) p580-7, ISSN 0364-5134 Journal Code: 6AE
Contract/Grant No.: AA07032, AA, NIAAA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Both alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor-mediated neurotoxicity and the induction of death-regulatory genes have been implicated in the pathophysiology of delayed ischemic neuronal injury. To assess the role of the antiapoptotic gene **Bcl-2** in the modulation of AMPA toxicity, we exposed neuron-enriched cultures from rat cerebral cortex to AMPA, in the absence or presence of an **antisense** oligodeoxynucleotide (ODN) directed against **Bcl-2** . AMPA produced concentration-dependent toxicity detected by a decrease in fluorescence of the redox indicator Alamar blue and by an increase in lactic acid dehydrogenase release. This effect was accompanied by the induction of **Bcl-2** protein expression, with maximal induction at 100 microM AMPA. A phosphorothioate **antisense** ODN against **Bcl-2** reduced the AMPA-stimulated induction of **Bcl-2** protein levels, detected by western blotting, by about 70%. In the presence of the **antisense** ODN, but not sense or scrambled ODNs, the toxicity of 100 microM AMPA was increased by about 60%. These findings suggest that induction of **Bcl-2** expression by AMPA may have a protective role to limit AMPA receptor-mediated neuronal damage and that modifying **Bcl-2** expression could have therapeutic potential in ischemia.

3/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09306896 97445801
The rescuing effect of nerve growth factor is the result of up-regulation of **bcl-2** in hyperoxia-induced apoptosis of a subclone of pheochromocytoma cells, PC12h.
Katoh S; Mitsui Y; Kitani K; Suzuki T
Radiation Safety Office, University of Tokyo Hospital, Japan.
Neuroscience letters (IRELAND) Aug 29 **1997**, 232 (2) p71-4, ISSN 0304-3940 Journal Code: N7N
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The rat pheochromocytoma cell line PC12 is useful for studying neuronal cell differentiation since this cell line differentiates into neuron-like cells in response to nerve growth factor (NGF). We demonstrated that PC12h cells, a subclone of PC12 cells, died under hyperoxia (50% O2). This cell death did not occur in the presence of antioxidant reagents. In the dead

cells, DNA fragmentation and chromatin condensation were observed, suggesting that hyperoxia-induced apoptosis via reactive oxygen species (ROS). NGF effectively suppressed this hyperoxia-induced apoptosis. Accordingly, the amounts of **bcl-2**, a proto-oncogene product, increased in the cells rescued from apoptosis by NGF. Furthermore, **bcl-2 antisense** oligonucleotide canceled this rescuing effect of NGF. The present findings indicate that NGF rescues PC12h cells from hyperoxia-induced apoptosis via up-regulation of **bcl-2**.

3/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09305353 98020650
Aberrant expression of **bcl-2** gene family in Down's syndrome brains.
Sawa A; Oyama F; Cairns NJ; Amano N; Matsushita M
Department of Neuropsychiatry, Faculty of Medicine, University of Tokyo, Japan. akira@welchlink.welch.jhu.edu
Brain research. Molecular brain research (NETHERLANDS) Aug **1997**, 48 (1) p53-9, ISSN 0169-328X Journal Code: MBR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Down's syndrome (DS) patient brains are known to develop prematurely the same degenerative changes as those seen in Alzheimer's disease (AD). On the assumption that the apoptotic mechanism is involved in the neuronal loss in DS, we have investigated the expression of the **bcl-2** gene family in DS brains and found marked alterations. The most prominent changes were in the temporal lobes where neuronal loss was greatest. Our findings suggest that a apoptotic process is involved in the neuronal loss in DS.

3/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09298320 98021579
Antisense therapy for lymphomas.
Cotter FE
Molecular Haematology Unit, Institute of Child Health, London, U.K.
Hematological oncology (ENGLAND) Feb **1997**, 15 (1) p3-11, ISSN 0278-0232 Journal Code: GB2
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The potential ability of **antisense** oligonucleotides to downregulate the expression of oncogenes involved in lymphoma, with minimal toxicity can be achieved. The possibility of combining **antisense** therapy such as **BCL-2 antisense** with chemotherapy will probably provide an interesting means of overcoming tumour cell resistance to chemotherapy in lymphoma and a range of other high **BCL-2** expressing malignancies. As additional **antisense** molecules targeting oncogenes involved in lymphomas become available, it will be possible to combine them with AO to enhance their efficacy, either targeting the same gene at two sites or more a combination of genes (for example, **BCL-2** and MYC in Burkitt's lymphoma). Of major importance are approaches to improve AO uptake into cells which is currently poor. Methods to improve **antisense** uptake into the cell are required and in addition a new generation of oligonucleotides free of the nonspecific thioate toxicities are required. AO are a dramatic new area of research and as such require much evaluation if they are to be applied maximally. Both in vitro and in vivo efficacy has been established. With care, novel therapies based on the biology of the malignant cell may be determined on a scientific basis and may help improve the treatment of patients with these diseases. Gene

silencing by **antisense** oligonucleotides has a role to play as demonstrated in lymphomas.

3/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09296806 98018288
Molecular aspects of breast and ovarian cancer.
Giannios J; Ioannidou-Mouzaka L
Agii Anargiri Hospital, Athens, Greece.
European journal of gynaecological oncology (ITALY) **1997**, 18 (5) p387-93, ISSN 0392-2936 Journal Code: ENA
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Extensive research has led to accumulation of common hereditary evidence concerning ovarian and breast cancer, suggesting that these two cancers can be considered as one type. Subsequently, women with breast cancer are susceptible to the risk of developing ovarian cancer. Highly expressed oncogenes such as **bcl-2** , HER2/neu and others or mutated suppressor genes such as p53 or BRCA1 have been characterised as hereditary susceptibility genes leading to syndromes such as breast/ovarian cancer syndrome, Li-Fraumeni and others. Furthermore, these genetic alterations can cause potent chemoresistance by inhibiting induction of apoptosis after DNA damage caused by chemotherapy and/or radiotherapy. Presently, molecular onco-biology has enabled us not only to detect susceptibility to ovarian and breast cancer but also ways to inhibit their further progression or even circumventing chemoresistance mechanisms after their development by gene therapy using delivery vectors such as liposomes or viruses, by which we can replace wild-type tumour suppressor genes or by using antigene, **antisense** oligonucleotides and **antisense** RNA leading to reduced oncogene expression, enabling induction of apoptosis after DNA damage into chemoresistant tumour cells. Furthermore efflux-genes such as MDR-1 or MRP can be circumvented, suicide-genes can be employed which can facilitate sensitivity by encoding enzymes capable of converting inactive forms of a drug into toxic antimetabolites and immunotherapy can be achieved, by transfection of tumour cells with adenoviral vectors encoding immunomodulators such as IL-2 or MHC molecules. Thus, molecular biology appears to be a very strong element for the screening, diagnosis, therapy and prognosis of ovarian and breast cancer. However, consistent future research is greatly needed because many points concerning ovarian and breast cancer genetics are still unknown. Finally, we strongly believe that gene therapy could be extremely useful when is combined with conventional therapy against ovarian and breast tumours.

3/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09281447 97373610
Angiotensin type 2 receptor dephosphorylates **Bcl-2** by activating mitogen-activated protein kinase phosphatase-1 and induces apoptosis.
Horiuchi M; Hayashida W; Kambe T; Yamada T; Dzau VJ
Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
Journal of biological chemistry (UNITED STATES) Jul 25 **1997**, 272 (30) p19022-6, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HL46631, HL, NHLBI; HL35252, HL, NHLBI; HL35610, HL, NHLBI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We examined the cellular and signaling mechanism of angiotensin II (Ang

II) type 2 (AT2) recept[redacted]induced apoptosis in PC12W (ra[redacted]heochromocytoma cell line) cells that express abundant AT2 receptor but not Ang II type 1 receptor. In these cells, nerve growth factor (NGF) inhibited the internucleosomal DNA fragmentation induced by serum depletion, whereas Ang II antagonized this NGF cell survival action and induced apoptosis. We studied the mechanism of NGF and AT2 receptor interaction on apoptosis by examining their effects on the survival factor **Bcl-2**. AT2 receptor activation did affect intracellular **Bcl-2** protein levels. **Bcl-2** phosphorylation was stimulated by NGF, whereas AT2 receptor activation blocked this NGF effect. Pretreatment with **antisense** oligonucleotide of mitogen-activated protein (MAP) kinase phosphatase-1 enhanced the effects of NGF on MAP kinase activation and **Bcl-2** phosphorylation but attenuated the inhibitory effects of AT2 receptor on MAP kinase, **Bcl-2** phosphorylation, and apoptosis. Taken together, these results suggest that MAP kinase plays a critical role in inhibiting apoptosis by phosphorylating **Bcl-2**. The AT2 receptor inhibits MAP kinase activation, resulting in the inactivation of **Bcl-2** and the induction of apoptosis.

3/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09274662 97267683

BCL-2 antisense therapy in patients with non-Hodgkin lymphoma.

Webb A; Cunningham D; Cotter F; Clarke PA; di Stefano F; Ross P; Corbo M; Dziewanowska Z

Lymphoma Unit, Royal Marsden Hospital, Sutton, Surrey.

Lancet (ENGLAND) Apr 19 **1997**, 349 (9059) p1137-41, ISSN 0140-6736 Journal Code: L0S

Languages: ENGLISH

Document type: CLINICAL TRIAL; CLINICAL TRIAL, PHASE I; JOURNAL ARTICLE

BACKGROUND: Overexpression of **BCL-2** is common in non-Hodgkin lymphoma and leads to resistance to programmed cell death (apoptosis) and promotes tumorigenesis. **Antisense** oligonucleotides targeted at the open reading frame of the **BCL-2** mRNA cause a specific down-regulation of **BCL-2** expression which leads to increased apoptosis. Lymphoma grown in laboratory animals responds to **BCL-2 antisense** oligonucleotides with few toxic effects. We report the first study of **BCL-2 antisense** therapy in human beings. METHODS: A daily subcutaneous infusion of 18-base, fully phosporothioated **antisense** oligonucleotide was administered for 2 weeks to nine patients who had **BCL-2** -positive relapsed non-Hodgkin lymphoma. Toxicity was scored by the common toxicity criteria, and tumour response was assessed by computed tomography scan. Efficacy was also assessed by quantification of **BCL-2** expression; **BCL-2** protein levels were measured by flow cytometry in samples from patients. FINDINGS: During the course of the study, the daily dose of **BCL-2 antisense** was increased incrementally from 4.6 mg/m2 to 73.6 mg/m2. No treatment-related toxic effects occurred, apart from local inflammation at the infusion site. In two patients, computed tomography scans showed a reduction in tumour size (one minor, one complete response). In two patients, the number of circulating lymphoma cells decreased during treatment. In four patients, serum concentrations of lactate dehydrogenase fell, and in two of these patients symptoms improved. We were able to measure **BCL-2** levels by flow cytometry in the samples of five patients, two of whom had reduced levels of **BCL-2** protein. INTERPRETATION: In patients with relapsing non-Hodgkin lymphoma, **BCL-2 antisense** therapy led to an improvement in symptoms, objective biochemical and radiological evidence of tumour response, and down-regulation of the **BCL-2** protein in some patients. Our findings are encouraging and warrant further investigations of **BCL-2 antisense** therapy in cancer treatment.

3/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09273566 97250532
Mitogen-activated protein kinase-mediated Fas apoptotic signaling pathway.
Goillot E; Raingeaud J; Ranger A; Tepper RI; Davis RJ; Harlow E; Sanchez I
Massachusetts General Hospital Cancer Center, Charlestown 02129, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 1 **1997**, 94 (7) p3302-7, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Ligation of the cell surface receptor Fas/APO-1 (CD95) by its specific ligand or by anti-Fas antibodies rapidly induces apoptosis in susceptible cells. To characterize the molecular events involved in Fas-induced apoptosis, we examined the contribution of two subgroups of the mitogen-activated protein (MAP) kinase family, the Jun kinases or stress-activated protein kinases (JNKs/SAPKs) and the extracellular signal-regulated kinases (ERKs), in a Fas-sensitive neuroblastoma cell line. Here we show that both JNK and ERK protein kinases were activated upon Fas crosslinking through a Ras-dependent mechanism. Interference with either the JNK or ERK pathway by ectopic expression of dominant-interfering mutant proteins blocked Fas-mediated apoptosis. ERK activation was transient and associated with induced expression of the Fas receptor. In contrast, JNK activation was sustained and correlated with the onset of apoptosis. These data indicate that the ERK and the JNK groups of MAP kinases cooperate in the induction of cell death by Fas. Inhibition of Fas killing by an interleukin 1beta-converting enzyme (ICE)-like protease inhibitor peptide did not modify Fas-induced JNK activation upon Fas ligation. In contrast, changes in **Bcl-2** level due to expression of sense and **antisense** vectors influenced the sensitivity to Fas killing and Fas-induced JNK activation.

3/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09273565 97250531
Resistance to apoptosis in CTLL-2 cells constitutively expressing c-Myb is associated with induction of **BCL-2** expression and Myb-dependent regulation of **bcl-2** promoter activity.
Salomoni P; Perrotti D; Martinez R; Franceschi C; Calabretta B
Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, PA 19107-6799, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 1 **1997**, 94 (7) p3296-301, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: R01 CA46782, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
c-Myb, the cellular homologue of the transforming gene of the avian myeloblastosis virus, is preferentially expressed in all hematopoietic lineages, including T and B lymphocyte lineages. In T lymphocytes, c-Myb expression appears to be required for cell cycle progression and proliferation. To further investigate the role of c-Myb in T cell proliferation and survival, interleukin (IL) 2-dependent CTLL-2 cells were transfected with a constitutively active c-myb or with a c-myb **antisense** construct able to down-regulate endogenous Myb levels, and the transfectants were assessed for proliferation and survival in low

concentrations of IL-2 and for susceptibility to dexamethasone-induced apoptosis. Compared with control cells, CTLL-2 cells constitutively expressing c-Myb proliferate in low concentrations of IL-2 and are less susceptible to apoptosis induced by IL-2 deprivation or treatment with dexamethasone. In contrast, cells transfected with an **antisense** c-myb construct do not proliferate in low concentrations of IL-2 and undergo apoptosis upon IL-2 deprivation or dexamethasone treatment more rapidly than parental cells. Overexpression of c-Myb was accompanied by up-regulation of **BCL-2** expression. In transient transfection assays, the murine **bcl-2** promoter was efficiently transactivated by c-Myb, but such effect was observed also in cells transfected with a DNA binding-deficient c-myb construct. Moreover, in gel retardation assays, a 38-bp oligomer in the shortest **bcl-2** promoter segment regulated by c-Myb formed a specific complex with nuclear extracts from c-Myb-transfected CTLL-2 cells. Thus, these results strongly suggest that c-Myb, in addition to regulating T cell proliferation, protects T lymphocytes from apoptosis by induction of **BCL-2** expression, which involves a c-Myb-dependent mechanism of promoter regulation.

3/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09262385 97442404

Protein kinase CbetaII activation by 1-beta-D-arabinofuranosylcytosine is antagonistic to stimulation of apoptosis and Bcl-2alpha down-regulation.

Whitman SP; Civoli F; Daniel LW
Department of Biochemistry, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157-1016, USA.

Journal of biological chemistry (UNITED STATES) Sep 19 **1997**, 272 (38) p23481-4, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA48995, CA, NCI; CA43297, CA, NCI; CA67717, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE

1-beta-D-Arabinofuranosylcytosine (ara-C) stimulates the formation of both diglyceride and ceramide in the acute myelogenous leukemia cell line HL-60 (Strum, J. C., Small, G. W., Pauig, S. B., and Daniel, L. W. (1994) J. Biol. Chem 269, 15493-15497). ara-C also causes apoptosis in HL-60 cells which can be mimicked by exogenous ceramide. However, the signaling role for ara-C-induced diacylglycerol (DAG) is not defined. We found that **Bcl-2** levels were increased by treatment of HL-60 cells with exogenous DAG or 12-O-tetradecanoylphorbol-13-acetate (TPA). In contrast, exogenous ceramide treatment caused a decrease in cellular **Bcl-2** levels. Thus, ara-C stimulates the synthesis of two second messengers with opposing effects on **Bcl-2**. Since the effects of ara-C-induced DAG could be due to protein kinase C (PKC) activation, we determined the effects of ara-C on PKC isozymes. ara-C caused an increase in membrane-bound PKCbetaII (but not PKCalpha or PKCdelta). ara-C or TPA-induced translocation of PKCbetaII was inhibited by 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine (ET-18-OCH3), and ara-C-induced apoptosis was stimulated by pretreatment of the cells with ET-18-OCH3. ET-18-OCH3 also inhibited stimulation of **Bcl-2** by TPA and enhanced the decrease in **Bcl-2** observed in ara-C-treated cells. These data indicate that ara-C-induced apoptosis is limited by ara-C-stimulated PKCbetaII through effects on **Bcl-2**. To further determine the role of PKC, we used **antisense** oligonucleotides directed toward PKCbetaII. The **antisense**, but not the sense, oligonucleotide inhibited PKCbetaII activation and enhanced ara-C-induced apoptosis. These data demonstrate that the stimulation of apoptosis by ara-C is self-limiting and can be enhanced by inhibition of PKC.

3/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09261914 97466969

Bcl-2 is overexpressed and alters the threshold for apoptosis in a cholangiocarcinoma cell line.

Harnois DM; Que FG; Celli A; LaRusso NF; Gores GJ

Center for Basic Research in Digestive Diseases, Division of Gastroenterology and Internal Medicine, Mayo Medical School, Clinic and Foundation, Rochester, MN 55905, USA.

Hepatology (UNITED STATES) Oct **1997**, 26 (4) p884-90, ISSN 0270-9139 Journal Code: GBZ

Contract/Grant No.: DK 41876, DK, NIDDK; DK 24031, DK, NIDDK; CA 15083-23F3.2, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Cholangiocarcinoma is a malignant neoplasm originating from cholangiocytes. The mechanisms responsible for oncogenesis of cholangiocytes are unknown. Resistance to apoptosis, especially by altered expression of B-cell lymphoma/leukemia 2 (**Bcl-2**) family members, has been implicated as a mechanism contributing to malignant transformation. Thus, our aim was to test the hypothesis that altered expression of **Bcl-2** family members by cholangiocarcinoma cells renders them resistant to apoptosis. We compared the apoptotic threshold and expression of the **Bcl-2** protein family members, **Bcl-2** , Bcl-XL, and Bax, in two human cell lines: 1) nonmalignant human cholangiocytes immortalized by transfection with the simian virus 40 (SV 40) large T antigen; and 2) a malignant human cholangiocarcinoma cell line. Apoptosis was induced pharmacologically using beauvericin. **Bcl-2** , Bcl-x long, and Bax protein expression were evaluated by immunoblot analysis, and **Bcl-2** expression was modulated using **antisense** technology. The cholangiocyte and malignant/nonmaligant phenotype of both cell lines was verified using both in vitro and in vivo approaches. Beauvericin induced apoptosis of nonmalignant cholangiocytes in a concentration- (0 to 25 micromol/L) and time- (0 to 6 hours) dependent manner. In contrast, malignant cholangiocytes were resistant to apoptosis. Although expression of Bcl-x long and Bax protein were similiar in the two cell lines, **Bcl-2** protein expression was 15-fold greater in malignant than in nonmalignant cholangiocytes. An 18 mer **bcl-2** **antisense** oligonucleotide reduced expression of **Bcl-2** protein by 50% and increased the rate of beauvericin-induced apoptosis more than threefold in the malignant cells. Our results support the hypothesis that resistance to apoptosis by overexpression of **Bcl-2** may be a feature of cholangiocarcinoma.

3/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09245317 97434297

Development of a hammerhead **ribozyme** against **bcl-2**. I. Preliminary evaluation of a potential gene therapeutic agent for hormone-refractory human prostate cancer.

Dorai T; Olsson CA; Katz AE; Buttyan R

Department of Urology, College of Physicians and Surgeons of Columbia University, New York, New York 10032, USA.

Prostate (UNITED STATES) Sep 1 **1997**, 32 (4) p246-58, ISSN 0270-4137 Journal Code: PB4

Languages: ENGLISH

Document type: JOURNAL ARTICLE

BACKGROUND: The **bcl-2** oncoprotein suppresses apoptosis and, when overexpressed in prostate cancer cells, makes these cells resistant to

a variety of therapeutic agents, including hormonal ablation. Therefore, **bcl-2** provides a strategic target for the development of gene knockout therapies to treat human prostate cancers. Towards this end, we have synthesized an anti-**bcl-2** gene therapeutic reagent based on **ribozyme** technology and have tested its effectiveness against **bcl-2** mRNA in vitro and in vivo. METHODS: A divalent hammerhead **ribozyme** was constructed by recombining two catalytic RNA domains into an **antisense** segment of the coding region for human **bcl-2** mRNA. A disabled **ribozyme** lacking catalytic activity was also constructed as a control reagent for our experiments. The **ribozymes** were tested for endonucleolytic activity against synthetic and natural **bcl-2** mRNAs. Simple transfection procedures were then utilized to introduce the **ribozymes** into cultured prostate cancer cells (LNCaP derivatives). We measured the effects of the **ribozymes** on endogenous expression of **bcl-2** mRNA and protein in these cells as well as their ability to induce apoptosis. RESULTS: The functional but not the disabled **ribozyme** was able to rapidly degrade **bcl-2** mRNA in vitro, without the requirement for any other cellular protein or factor. When directly transfected into LNCaP cell variants, it significantly reduced **bcl-2** mRNA and protein levels within 18 hr of treatment. This activity was sufficient to induce apoptosis in a low-**bcl-2**-expressing variant of LNCaP, but not in a high-**bcl-2**-expressing LNCaP line. For the high-**bcl-2**-expressing variant, however, it did restore the ability to genetically respond to a secondary apoptotic agent, phorbol ester, as evidenced by the renewed ability of phorbol ester to induce NGF1A mRNA in these cells. CONCLUSIONS: This study supports the potential utility of an anti-**bcl-2** **ribozyme** reagent for reducing or eliminating **bcl-2** expression from hormone-refractory prostate cancer cells and for killing prostate cancer cells. As such, it is the first step toward an effective gene therapy against hormone-refractory human prostate cancers.

3/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09235900 97422560

Heat shock protein 65 induced by gammadelta T cells prevents apoptosis of macrophages and contributes to host defense in mice infected with Toxoplasma gondii.

Hisaeda H; Sakai T; Ishikawa H; Maekawa Y; Yasutomo K; Good RA; Himeno K

Department of Parasitology and Immunology, The University of Tokushima School of Medicine, Japan.

Journal of immunology (UNITED STATES) Sep 1 **1997**, 159 (5) p2375-81, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: 5628-12

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We previously reported that gammadelta T cells mediate the expression of endogenous heat shock protein 65 (HSP65) in macrophages of mice with acquired resistance against infection with Toxoplasma gondii. We show here that HSP65 contributes to protective immunity by preventing apoptosis of infected macrophages. Macrophages of BALB/c mice, which readily acquired resistance to T. gondii infection with the low virulence Beverley strain, strongly expressed HSP65, and only a few of these macrophages underwent apoptosis. On the other hand, the BALB/c mice were susceptible to the infection with the high virulence RH strain of T. gondii; their macrophages did not express HSP65 and did undergo apoptosis. Mice depleted of gammadelta T cells using a mAb specific for TCR-gammadelta became highly susceptible to infection even with the Beverley strain. In these mice, HSP65 expression was markedly suppressed, and their infected macrophages died via apoptosis. Apoptosis was induced in cultured macrophages or macrophage cell lines after infection in vitro with the RH strain, whereas apoptosis was prevented when HSP65 was induced in these cells, before

infection, by activation with IFN-gamma and TNF-alpha. However, apoptosis associated with infection by T. gondii RH strain was not prevented when HSP65 synthesis was inhibited by introducing an **antisense** oligonucleotide for this protein into the cells before activation with IFN-gamma plus TNF-alpha. Thus, HSP65 appears to contribute to immunity by preventing the apoptosis of infected macrophages, and the high virulence Toxoplasma appears to have mechanisms that allow these organisms to evade the host defense system by interfering with HSP65 expression.

3/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09209789 97368335
The **antisense bcl-2**-IgH transcript is an optimal target for synthetic oligonucleotides.
Morelli S; Delia D; Capaccioli S; Quattrone A; Schiavone N; Bevilacqua A; Tomasini S; Nicolin A
Department of Pharmacology, University of Milan, Milan, Italy.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jul 22 **1997**, 94 (15) p8150-5, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In most human follicular B cell lymphomas the **bcl-2** gene is up-regulated as a result of the t(14;18) chromosomal translocation generating a hybrid **bcl-2** -IgH mRNA. Recently, we have identified in t(14;18)-positive cells a **bcl-2**-IgH mRNA in the **antisense** orientation, putatively responsible for the overexpression of **bcl-2**. Herein we show that this chimeric **antisense** transcript is an optimal target for synthetic oligodeoxynucleotides (ODNs). A variety of sense-oriented oligonucleotides have been designed that target the **antisense** transcript in regions endowed with a sequence specificity presumably restricted to an individual cell line (the **bcl -2**-IgH fusion regions) or extended to all t(14;18) cells (the ectopic **bcl-2** segment upstream from the major breakpoint region and the IgH segment). All sense-oriented ODNs complementary to the **antisense** transcript induced an early strong inhibition of cell growth and a late fulminant cell death. As expected, the activity of ODNs targeting the fusion region was restricted to each individual cell line, whereas the activity of all ODNs targeting the common **bcl-2** and IgH segments was extended to all t(14;18) cell lines tested. These sense ODNs were not effective in untranslocated cell lines. **Antisense**-oriented ODNs, complementary to the **bcl-2**-IgH mRNA, and control ODNs (scrambled, inverted, or mismatched) were biologically ineffective. The selectivity and efficacy of all sense ODNs tested provide support for the development of therapeutic ODNs targeting the **bcl-2**-IgH **antisense** transcript expressed in human follicular lymphomas.

3/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09194208 97315947
Antisense down-regulation of metallothionein induces growth arrest and apoptosis in human breast carcinoma cells.
Abdel-Mageed A; Agrawal KC
Department of Pharmacology, Tulane Cancer Center, Tulane University Medical Center, New Orleans, Louisiana, USA.
Cancer gene therapy (UNITED STATES) May-Jun **1997**, 4 (3) p199-207 , ISSN 0929-1903 Journal Code: CE3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The association of increased metallothionein (MT) gene expression in breast cancer with metastasis and poor prognosis has led us to investigate the hypothesis that inhibition of MT gene expression may elicit antiproliferative effects in breast carcinoma MCF7 cells. To monitor the effect of downregulation of MT protein on growth, MCF7 cells were transiently transfected by electroporation with an 18-mer MT **antisense** phosphorothioate oligomer (AO) or an 18-mer random oligomer (RO). The MT-AO is complementary to the region 7 bases downstream from the AUG translational start site of the hMT-IIA gene. Transfection of MCE7 cells with the AO inhibited cell growth by 50-60% at 72 hours when compared to control cells or the cells transfected with RO. The AO-induced growth inhibition was associated with alterations in morphology suggestive of apoptotic cell death. This was further confirmed by DNA linker cleavage into oligonucleosomal fragments and decreased **bcl-2** protein levels in AO-transfected cells as opposed to the RO-transfected cells. Reverse transcriptase polymerase chain reaction analysis showed that AO induced a 2-fold increase in the levels of c-fos and p53 transcripts in comparison to RO which had no significant effect. Conversely, c-myc transcripts were decreased by 2.5-fold in the AO-transfected cells when compared to the controls. Furthermore, MCF7 cells transfected with an expression plasmid pBAcNEO-sMT-IIA encompassing human MT-IIA cDNA, constitutively driven by beta-actin promotor, caused a 2.5-fold increase in intracellular levels of MT, as judged by PCR and western blot analysis, in comparison to the cells transfected with pBAcNEO plasmid. In contrast to the AO-induced growth inhibition, overexpression of cytoplasmic MT increased the cell multiplication by 2-fold compared with control cells or the cells transfected with the control plasmid 72 hours post-transfection. Moreover, the effects of AO on oncogene expression were reversed on increased expression of MT. These data suggest that overexpression of MT potentiates the growth of MCF7 cells, whereas downregulation of MT elicits antiproliferative effects.

3/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09189790 97374427
Promise and problems of **Bcl-2** **antisense** therapy [editorial; comment]
Reed JC
Journal of the National Cancer Institute (UNITED STATES) Jul 16 **1997**, 89 (14) p988-90, ISSN 0027-8874 Journal Code: J9J
Comment on J Natl Cancer Inst 1997 Jul 16;89(14):1027-36
Languages: ENGLISH
Document type: COMMENT; EDITORIAL; REVIEW; REVIEW, TUTORIAL

3/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09189782 97374435
Induction of apoptosis in small-cell lung cancer cells by an **antisense** oligodeoxynucleotide targeting the **Bcl-2** coding sequence [see comments]
Ziegler A; Luedke GH; Fabbro D; Altmann KH; Stahel RA; Zangemeister-Wittke U
University Hospital Zurich, Department of Internal Medicine, Switzerland.
Journal of the National Cancer Institute (UNITED STATES) Jul 16 **1997**, 89 (14) p1027-36, ISSN 0027-8874 Journal Code: J9J
Comment in J Natl Cancer Inst 1997 Jul 16;89(14):988-90
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: The emergence of resistance to chemotherapy remains a major

problem in the treatment of patients with small-cell lung cancer. Elevated expression of **Bcl-2** , a protein that inhibits programmed cell death or apoptosis, has been associated with radiation and drug resistance and has been observed in the majority of small-cell lung cancer specimens and cell lines. PURPOSE: To test the hypothesis that **Bcl-2** expression levels are critical for inhibiting apoptosis in small-cell lung cancer cells, we used an **antisense** strategy to reduce **Bcl-2** expression in these cells in an attempt to restore the natural occurrence of apoptosis. METHODS: Thirteen **antisense** oligodeoxynucleotides (ODNs) targeting various regions of the **bcl-2** messenger RNA and a control scrambled-sequence ODN were tested to identify the most effective sequence(s) for reducing **Bcl-2** protein levels. Northern and western blot analyses were used to examine basal **bcl-2** messenger RNA and protein levels, respectively, in four human small-cell lung cancer cell lines (SW2, NCI-H69, NCI-H82, and NCI-N417). SW2 cells were treated with the **antisense** ODNs in the presence of cationic lipids (to facilitate uptake), and cytotoxic effects were measured by use of a cell viability assay. Flow cytometric analysis of DNA fragmentation and cell morphology was also performed. The cytotoxic effect of the most potent **antisense** ODN was also tested on the three other cell lines. RESULTS: The viability of SW2 cells was effectively reduced by ODNs that targeted the translation initiation and termination sites of the **bcl-2** messenger RNA, but ODN 2009 that targeted the coding region was the most cytotoxic. Treatment of SW2 cells with 0.15 microM ODN 2009 for 96 hours reduced their viability by 91% (95% confidence interval [CI] = 88%-94%) and caused a dose-dependent reduction in **Bcl-2** levels that became detectable 24 hours after treatment and persisted up to 96 hours; analysis of cellular morphology demonstrated that viability was reduced through apoptosis. Moreover, ODN 2009 at 0.15 microM was cytotoxic to NCI-H69, NCI-H82, and NCI-N417 cells, resulting in decreases in cell viability of 82% (95% CI = 78%-86%), 100%, and 100%, respectively, after 96 hours of treatment. The cytotoxic effects were inversely correlated with the basal **Bcl-2** levels in the cell lines (r = -9964). A control scrambled-sequence oligodeoxynucleotide had no statistically significant effect on the cell lines (P values ranging from .38 to .89). CONCLUSION: We have identified a novel **antisense** ODN sequence (ODN 2009) that effectively reduces the viability of small-cell lung cancer cells by reducing **Bcl-2** levels and facilitating apoptosis.

3/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09156835 97312646
Developmental expression of morphoregulatory genes in the mouse embryo: an analytical approach using a novel technology.
Craig JC; Eberwine JH; Calvin JA; Wlodarczyk B; Bennett GD; Finnell RH
Department of Veterinary Anatomy and Public Health, Texas A&M University, College Station 77843, USA.
Biochemical and molecular medicine (UNITED STATES) Apr **1997**, 60 (2) p81-91, ISSN 1077-3150 Journal Code: B3J
Contract/Grant No.: DE 11303, DE, NIDCR; ES 07165, ES, NIEHS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The molecular techniques of in situ transcription and **antisense** RNA amplification (IST/aRNA) have allowed for the monitoring of coordinate changes in the expression of multiple genes simultaneously. However, the analysis of their concurrent behavior during murine embryogenesis has been problematic. Studies involving the investigation of temporal and spatial gene expression during embryogenesis have focused solely on the analysis of isolated, single gene events. Such an approach has failed to provide an integrative picture of genetic control over the varied and complicated cellular processes governing embryogenesis. In order to interpret the

enormous amount of gene expression data generated by these procedures, we have attempted to develop an analytical framework employing the statistical concepts of principal components analysis (PCA). For the current study, we performed IST/aRNA on neural tubes dissected from the highly inbred LM/Bc murine strain collected during four gestational time periods. A subset of these genes, representing a partial signaling pathway in the developing neuroepithelium, was then subjected to PCA. Here, we report that PCA highlighted the transcriptional interplay among the genes p53, wee-1, Tgf beta-2, and **bcl-2** such that the combined reciprocal regulation of their gene products is suggestive of a predominant proliferative state for the developing neuroepithelium. The application of PCA to the gene expression data has elucidated previously unknown interrelationships among cell cycle genes, growth, and transcription factors on a transcriptional level during critical stages of neurulation. The information gleaned from this analysis, while not definitive, suggests distinct hypotheses to guide future research.

3/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09153861 97332626
Regulation of Fas-dependent activation-induced T cell apoptosis by cAMP signaling: a potential role for transcription factor NF-kappa B.
Ivanov VN; Lee RK; Podack ER; Malek TR
Department of Microbiology and Immunology, University of Miami School of Medicine, Florida 33101, USA.
Oncogene (ENGLAND) May 22 **1997**, 14 (20) p2455-64, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: RO1-CA4609, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
TCR-mediated activation of T cell hybridomas induces programmed cell death by a Fas-dependent pathway. We now show that costimulation of 2B4 cells, in the absence or presence of transgenic **Bcl-2**, with anti-CD3 epsilon and forskolin, an activator of cAMP signaling, resulted in antagonism of Fas-dependent activation-induced cell death that was always accompanied by selective downregulation of the nuclear levels of NF-kappa B p65-p50 (RelA-p50) transcription factor. Forskolin not only inhibited activation-induced cell death and NF-kappa B activation, but also suppressed expression of Fas and Fas ligand (Fas-L). Furthermore, NF-kappa B p65 **antisense** oligonucleotide down-regulated nuclear levels of NF-kappa B, inhibited cell surface expression of Fas-L and apoptosis of 2B4. Collectively, these finding demonstrate a potential role of NF-kappa B in the regulation of activation-induced apoptosis in T lymphocytes.

3/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09147089 97313416
Cytotoxicity and apoptosis produced by arachidonic acid in Hep G2 cells overexpressing human cytochrome P4502E1.
Chen Q; Galleano M; Cederbaum AI
Department of Biochemistry, Mount Sinai School of Medicine, New York, New York 10029, USA.
Journal of biological chemistry (UNITED STATES) Jun 6 **1997**, 272 (23) p14532-41, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: AA03312, AA, NIAAA; AA06610, AA, NIAAA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The goal of the current study was to evaluate the effects of arachidonic acid, as a representative polyunsaturated fatty acid, on the viability of a

Hep G2 cell line, which has been transduced to express human cytochrome P4502E1 (CYP2E1). Arachidonic acid produced a concentration- and time-dependent toxicity to Hep G2-MV2E1-9 cells, which express CYP2E1, but little or no toxicity was found with control Hep G2-MV-5 cells, which were infected with retrovirus lacking human CYP2E1 cDNA. In contrast to arachidonic acid, oleic acid was not toxic to the Hep G2-MV2E1-9 cells. The cytotoxicity of arachidonic acid appeared to involve a lipid peroxidation type of mechanism since toxicity was enhanced after depletion of cellular glutathione; formation of malondialdehyde and 4-hydroxy-2-nonenal was markedly elevated in the cells expressing CYP2E1, and toxicity was prevented by antioxidants such as alpha-tocopherol phosphate, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox), propylgall ate, ascorbate, and diphenylphenylenediamine, and the iron chelator desferrioxamine. Transfection of the Hep G2-MV2E1-9 cells with plasmid containing CYP2E1 in the sense orientation enhanced the arachidonic acid toxicity, whereas transfection with plasmid containing CYP2E1 in the **antisense** orientation decreased toxicity. The CYP2E1-dependent arachidonic acid toxicity appeared to involve apoptosis, as demonstrated by terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling and DNA laddering experiments. Trolox, which prevented toxicity of arachidonic acid, also prevented the apoptosis. Transfection with a plasmid containing **bcl-2** resulted in complete protection against the CYP2E1-dependent arachidonic acid toxicity. It is proposed that elevated production of reactive oxygen intermediates by cells expressing CYP2E1 can cause lipid peroxidation, which subsequently promotes apoptosis and cell toxicity when the cells are enriched with polyunsaturated fatty acids such as arachidonic acid. The Hep G2-MV2E1-9 cells appear to be a valuable model to study interaction between CYP2E1, polyunsaturated fatty acids, reactive radicals, and the consequence of these interactions on cell viability and to reproduce several of the key features associated with ethanol hepatotoxicity in the intragastric infusion model of ethanol treatment.

3/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09134610 97246712

Glucose deprivation-induced cytotoxicity in drug resistant human breast carcinoma MCF-7/ADR cells: role of c-myc and **bcl-2** in apoptotic cell death.

Lee YJ; Galoforo SS; Berns CM; Tong WP; Kim HR; Corry PM

Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan 48073, USA.

Journal of cell science (ENGLAND) Mar **1997**, 110 (Pt 5) p681-6, ISSN 0021-9533 Journal Code: HNK

Contract/Grant No.: CA48000, CA, NCI; CA44550, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We investigated the effect of glucose deprivation treatment on clonogenicity in multidrug-resistant human breast carcinoma MCF-7/ADR cells. Survival of MCF-7/ADR cells decreased exponentially up to 8 hours of incubation in the glucose-free medium. The surviving fraction of these cells for 8 hours of glucose-deprivation treatment was 1.5 x 10(-3). Photomicrographs and gel electrophoresis data suggest that glucose deprivation-induced cell death is associated with apoptosis. Data from western and northern blots showed an induction of c-myc gene expression during treatment with glucose-free medium in MCF-7/ADR cells. MCF-7/ADR cells transfected with c-myc **antisense** oligodeoxynucleotides became resistant to glucose deprivation-induced apoptosis. Overexpression of **bcl-2** gene protected MCF-7/ADR cells from this apoptotic cell death. Taken together, these results indicate that c-myc expression is a necessary component of glucose-free medium induced apoptosis and **bcl-2** prevents apoptotic death induced by c-myc.

3/3,AB/72 (Item 72 [redacted]m file: 155)
DIALOG(R)File 155:MEDLINE(R)

09107596 97275928
Antisense oligonucleotides as therapeutics for malignant diseases.
Ho PT; Parkinson DR
Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute, Rockville, MD 20852, USA.
Seminars in oncology (UNITED STATES) Apr **1997**, 24 (2) p187-202, ISSN 0093-7754 Journal Code: UN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
The continued progress in our understanding of the biology of neoplasia and in the identification, cloning, and sequencing of genes critical to tumor cell function permits the exploitation of this information to develop specific agents that may directly modulate the function of these genes or their protein products. **Antisense** oligonucleotides are being investigated as a potential therapeutic modality that takes direct advantage of molecular sequencing. The **antisense** approach uses short oligonucleotides designed to hybridize to a target mRNA transcript through Watson-Crick base pairing. The formation of this oligonucleotide: RNA heteroduplex results in mRNA inactivation and consequent inhibition of synthesis of the protein product. A fundamental attraction of the **antisense** approach is that this method potentially may be applied to any gene product, in theory, for the treatment of malignant and non-malignant diseases. However, this simple and attractive model has proven to be much more complex in practice. A number of important challenges in the preclinical development of **antisense** oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture. Although the biological activity of an oligonucleotide against its molecular target is theoretically sequence-dependent, the animal pharmacokinetics and toxicology of phosphorothioate analogues directed against vastly disparate gene products appear relatively non-sequence-specific. In oncology, a number of clinical trials have been initiated with **antisense** oligonucleotides directed against molecular targets including: p53; **bcl-2** ; raf kinase; protein kinase C-alpha; c-myb. The experience gained from these early clinical trials will be applicable to the next generation of **antisense** agents in development. These may include molecules with novel backbones or other structural modifications, chimeric oligonucleotides, or peptide nucleic acids. Continued progress in this arena will require that many of the preclinical challenges confronting **antisense** development are satisfactory resolved.

3/3,AB/73 (Item 73 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09106586 97256684
Pharmacokinetics of G3139, a phosphorothioate oligodeoxynucleotide **antisense** to **bcl-2**, after intravenous administration or continuous subcutaneous infusion to mice.
Raynaud FI; Orr RM; Goddard PM; Lacey HA; Lancashire H; Judson IR; Beck T ; Bryan B; Cotter FE
Cancer Research Campaign Centre for Cancer Therapeutics, The Institute of Cancer Research, Sutton, Surrey, United Kingdom.
Journal of pharmacology and experimental therapeutics (UNITED STATES) Apr **1997**, 281 (1) p420-7, ISSN 0022-3565 Journal Code: JP3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

An 18-mer full-phosphorothioate oligonucleotide with sequence **antisense** to the first six codons of the open reading frame of **bcl-2** (G3139) has shown efficacy against the DoHH2 lymphoma implanted in severe combined immunodeficient mice. This study evaluated the pharmacokinetics of 35S-labeled G3139 in female BALB/c mice after single i.v. bolus administration or s.c. infusion for 1 week. After 100 microg i.v. bolus (approximately 5 mg/kg), the radioactivity was rapidly distributed and eliminated, with low blood levels 6 hr after administration. Most of the initial plasma radioactivity was protein bound (98% at 5 min). Tissue to plasma ratios were 87 for kidney, 17 for liver, 5 for spleen, 2.5 for heart and lung and 3.5 for gut. High-performance liquid chromatographic determination of G3139 showed triexponential kinetics, with alpha, beta and gamma half-lives of 5 min, 37 min and 11 hr, respectively. After 106 microg/day s.c. infusion, plasma steady state was reached by day 3, when half of the radioactivity was protein bound and 66 to 86% of the radioactivity was associated with parent drug (0.9 microg/ml). The plasma half-life of elimination for G3139 was 22 hr. Tissue to plasma ratios were similar to those after i.v. bolus administration, but accumulation was observed in all organs including bone marrow, where the levels reached were in the cytotoxic range. G3139 was metabolized to at least three different products, all observed in plasma, liver and kidney. Two metabolites eluted before the parent compound and one after the parent compound. There was greater degradation in the liver 6 hr after i.v. administration than at 24 hr, 48 hr, 3 days and 7 days after s.c. administration. In the kidney, most radioactivity was G3139. All degradation products were found in the urine but only traces of parent drug were eliminated. After both routes of administration, most of the radioactivity was eliminated in the urine and to a lesser extent in the feces. Significantly more radioactivity was excreted in the urine after i.v. bolus, compared with s.c. infusion (33% on day 1 and 55% by day 3 for i.v. vs. 7.2% on day 1 and 12.9% by day 3 for s.c.). These data show that s.c. infusion resulted in less excretion and metabolism of the administered dose.

3/3,AB/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09097718 97223337

Expression of Epstein-Barr virus latent membrane protein 1 protects Jurkat T cells from apoptosis induced by serum deprivation.

Kawanishi M
Department of Microbiology, Graduate School of Medicine, Kyoto University, Japan.

Virology (UNITED STATES) Feb 17 **1997**, 228 (2) p244-50, ISSN 0042-6822 Journal Code: XEA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

It has been generally accepted that inhibition of apoptosis is important in the development of malignancy. To determine whether Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1), the virus-coded transforming oncogene product, has an anti-apoptotic function in non-B-cells, Jurkat T cells were transfected with the LMP1-expression vector pSV2gptMTLM consisting of the human metallothionein promoter and were selected for mycophonolic acid resistance. LMP1-expressing clones of Jurkat cells showed resistance to apoptosis induced by serum deprivation. In LMP1-expressing clones, although the levels of **Bcl-2** and Bax were similar to those in the clones of vector transfectants or parental cells, c-Myc expression was significantly depressed. Down-regulation of c-Myc by LMP1 was confirmed by using LMP1-expressing clones treated with CdCl2. Addition of c-myc **antisense** oligonucleotides to Jurkat cells specifically inhibited apoptosis induced by serum deprivation at the concentrations which suppressed c-Myc expression. These results suggest that LMP1 expression and subsequent down-regulation of c-Myc protect Jurkat T cells from apoptosis induced by serum deprivation. The significance of the

anti-apoptotic function of LMP1 in non-B, Jurkat T cells is discussed in relation to the pathogenesis of EBV malignancy.

3/3,AB/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09094543 97258788
Phenytoin-induced teratogenesis: a molecular basis for the observed developmental delay during neurulation.
Bennett GD; Lau F; Calvin JA; Finnell RH
Department of Veterinary Anatomy and Public Health, College of Veterinary Medicine, Texas A&M University, College Station 77843-4458, USA.
Epilepsia (UNITED STATES) Apr **1997**, 38 (4) p415-23, ISSN 0013-9580 Journal Code: EIX
Contract/Grant No.: DE11303, DE, NIDCR; ES07165, ES, NIEHS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
PURPOSE: We wished to determine whether chronic phenytoin (PHT) exposure could impair neural development and if any morphological alterations could be linked to changes in gene expression. METHODS: Pregnant SWV mice were chronically administered PHT 40 mg/kg/day from gestational day (GD) 0:12 (day:h) until they were killed at various timepoints throughout neural tube closure (NTC). At each timepoint, embryos from both treated and control dams were collected and scored for their progression through NTC. The neural tubes were then isolated and subjected to in situ transcription (IST) and **antisense** RNA amplification procedures. Using these techniques, we examined the expression of 10 genes: N-cadherin (Ncad), collagen type IV (col-IV), **bcl-2** , c-jun, PAX-3, collular retinol binding protein-2 (CRBP-2), retinoic acid receptor alpha (RAR alpha), transforming growth factor(beta2) (TGF(beta2)), wee-1, and EMX-2. RESULTS: Chronic PHT exposure not only caused a delay in NTC whereby exposed embryos lagged behind the controls at each collection timepoint, but also significantly altered the expression of specific genes at distinct times during NTC. Early in NTC, PHT induced a significant reduction in the expression of N-cad, col-IV, and c-jun in exposed embryos as compared with controls. In contrast, during the midstages of NTC, the only significant molecular alterations observed in the PHT-exposed embryos was the continued decreased expression of col-IV and an increase in CRBP-2 expression. Finally, in the latter stages of NTC, PHT caused a significant reduction in the expression of **bcl-2** , RAR alpha, TGF(beta2), EMX-2, and PAX-3. CONCLUSIONS: These results show that although the effects of PHT are morphologically subtle, causing a delay in the development of the neural tube, this delay is accompanied by alterations in critical genes at crucial times of neural development that may account for the observed neurological deficits often associated with PHT exposure.

3/3,AB/76 (Item 76 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09085757 97213788
Neuroprotective action of cycloheximide involves induction of **bcl-2** and antioxidant pathways.
Furukawa K; Estus S; Fu W; Mark RJ; Mattson MP
Sanders-Brown Research Center on Aging, University of Kentucky, Lexington 40536, USA.
Journal of cell biology (UNITED STATES) Mar 10 **1997**, 136 (5) p1137-49, ISSN 0021-9525 Journal Code: HMV
Contract/Grant No.: NS29001, NS, NINDS; NS30583, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The ability of the protein synthesis inhibitor cycloheximide (CHX) to

prevent neuronal death in different paradigms has been interpreted to indicate that the cell death process requires synthesis of "killer" proteins. On the other hand, data indicate that neurotrophic factors protect neurons in the same death paradigms by inducing expression of neuroprotective gene products. We now provide evidence that in embryonic rat hippocampal cell cultures, CHX protects neurons against oxidative insults by a mechanism involving induction of neuroprotective gene products including the antiapoptotic gene **bcl-2** and antioxidant enzymes. Neuronal survival after exposure to glutamate, FeSO4, and amyloid beta-peptide was increased in cultures pretreated with CHX at concentrations of 50-500 nM; higher and lower concentrations were ineffective. Neuroprotective concentrations of CHX caused only a moderate (20-40%) reduction in overall protein synthesis, and induced an increase in c-fos, c-jun, and **bcl-2** mRNAs and protein levels as determined by reverse transcription-PCR analysis and immunocytochemistry, respectively. At neuroprotective CHX concentrations, levels of c-fos heteronuclear RNA increased in parallel with c-fos mRNA, indicating that CHX acts by inducing transcription. Neuroprotective concentrations of CHX suppressed accumulation of H2O2 induced by FeSO4, suggesting activation of antioxidant pathways. Treatment of cultures with an **antisense** oligodeoxynucleotide directed against **bcl-2** mRNA decreased **Bcl-2** protein levels and significantly reduced the neuroprotective action of CHX, suggesting that induction of **Bcl-2** expression was mechanistically involved in the neuroprotective actions of CHX. In addition, activity levels of the antioxidant enzymes Cu/Zn-superoxide dismutase, Mn-superoxide dismutase, and catalase were significantly increased in cultures exposed to neuroprotective levels of CHX. Our data suggest that low concentrations of CHX can promote neuron survival by inducing increased levels of gene products that function in antioxidant pathways, a neuroprotective mechanism similar to that used by neurotrophic factors.

3/3,AB/77 (Item 77 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09066676 97163456

IL-5 but not interferon-gamma (IFN-gamma) inhibits eosinophil apoptosis by up-regulation of **bcl-2** expression.

Ochiai K; Kagami M; Matsumura R; Tomioka H

Department of Internal Medicine, Toho University School of Medicine, Sakura Hospital, Chiba, Japan.

Clinical and experimental immunology (ENGLAND) Jan **1997**, 107 (1) p198-204, ISSN 0009-9104 Journal Code: DD7

Languages: ENGLISH

Document type: JOURNAL ARTICLE

In order to determine regulatory mechanisms of eosinophil apoptosis, we examined the effect of recombinant IL-5 and interferon-gamma (IFN-gamma) on eosinophil apoptosis and **bcl-2** expression. rhIL-5 (2.5 ng/ml) significantly inhibited eosinophil apoptosis in 96 h in vitro culture compared with medium only-cultured eosinophils (89.4 +/- 3.6% versus 31.3 +/- 12.2% (mean +/- s.d.); n = 7, P < 0.05). Further, rhIL-5 significantly increased **bcl-2** protein and mRNA expression on cultured eosinophils. A phosphorothioate **antisense** oligonucleotide targeted at the ATG translation initiation codon of **bcl-2** (10(-5) M) could significantly block the supportive effect of rhIL-5 (0.25 ng/ml) for eosinophil survival compared with sense cDNA of **bcl-2** on 96 h culture (inhibition rate 28.01 +/- 4.56% versus 0.07 +/- 1.73%; n = 4, P < 0.05). In contrast, rhIFN-gamma (100 U/ml) significantly inhibited eosinophil apoptosis on 96 h in vitro culture (72.7 +/- 10.5%; n = 7, P < 0.05), but did not significantly up-regulate **bcl-2** protein and mRNA. These results indicate that IL-5 has inhibitory effects on eosinophil apoptosis by regulation of **bcl-2** expression.

3/3,AB/78 (Item 78 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09055830 97098750
Critical role of Lyn kinase in inhibition of neutrophil apoptosis by granulocyte-macrophage colony-stimulating factor.
Wei S; Liu JH; Epling-Burnette PK; Gamero AM; Ussery D; Pearson EW; Elkabani ME; Diaz JI; Djeu JY
Immunology Program, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida College of Medicine, Tampa 33612, USA.
Journal of immunology (UNITED STATES) Dec 1 **1996**, 157 (11) p5155-62, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: CA63724, CA, NCI; AI33674, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The signal pathway for control of apoptosis in human neutrophils is currently unknown. In this study, we provide the first evidence that a Src family tyrosine kinase, Lyn, plays a key role in inhibition polymorphonuclear (PMN) cell death. Several nuclear proteins associated with apoptosis, i.e., p53, cdc2, and Rb, were absent from PMN. **Bcl-2**, known to inhibit apoptosis, was also not expressed. Programmed cell death that rapidly occurred in PMN could be arrested by granulocyte-macrophage CSF (GM-CSF), but this activation did not induce p53, cdc2, retinoblastoma, or **Bcl-2** expression. Instead, GM-CSF produced a rapid activation of Lyn and Hck, but not Fgr, tyrosine phosphorylation within 1 min. Co-immunoprecipitation studies indicated that only Lyn, but not Hck, was physically coupled to GM-CSF receptor. By histologic assessment and evaluation of DNA fragmentation, only **antisense** Lyn, but not **antisense** Hck or **antisense** Fgr, could reverse the cell survival advantage provided by GM-CSF. Therefore, the physical coupling of Lyn to GM-CSF receptor and its early activation are required for inhibition or delay of apoptosis in PMN.

3/3,AB/79 (Item 79 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09013915 97054648
Distinct mechanisms for rescue from apoptosis in Ramos human B cells by signaling through CD40 and interleukin-4 receptor: role for inhibition of an early response gene, Berg36.
Ning ZQ; Norton JD; Li J; Murphy JJ
Infection and Immunity Research group, King's College London, GB.
European journal of immunology (GERMANY) Oct **1996**, 26 (10) p2356-63, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The role of interleukin-4 (IL-4) and CD40 signaling in negative regulation of apoptosis in human Ramos B cells induced in response to different agents was investigated. CD40 ligation protected cells from apoptosis induced by calcium ionophore through an initial, rapid and apparently **Bcl-2** -independent mechanism, associated with up-regulation of Bcl-XL. However, rescue from apoptosis induced by inhibition of macromolecular synthesis required several hours of prior stimulation with CD40 ligand/antibody and was accompanied by up-regulation of **Bcl-2**. In contrast, IL-4 did not up-regulate **Bcl-2** or Bcl-XL and did not inhibit apoptosis induced by inhibitors of macromolecular synthesis. However, IL-4 did protect Ramos cells from apoptosis induced by calcium ionophore and this effect was accompanied by inhibition of ionophore-induced expression of an immediate early gene encoding a 36-kDa zinc-finger protein, Berg36. **Antisense** blockade of Berg36 expression partially inhibited ionophore-induced apoptosis to an

extent commensurate with the level of IL-4 protection, implicating Berg36 function as a requirement for apoptosis induced through calcium signaling and as a target for IL-4 through which this cytokine inhibits apoptosis in Ramos B cells. These distinct mechanisms for rescue from apoptosis by CD40 and IL-4 may help explain the co-operative roles of these T cell-derived signals for B cell survival.

3/3,AB/80 (Item 80 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09002249 96292232
A **bcl-2**/IgH **antisense** transcript deregulates **bcl-2** gene expression in human follicular lymphoma t(14;18) cell lines.
Capaccioli S; Quattrone A; Schiavone N; Calastretti A; Copreni E; Bevilacqua A; Canti G; Gong L; Morelli S; Nicolin A
Institute of General Pathology, University of Florence, Italy.
Oncogene (ENGLAND) Jul 4 **1996**, 13 (1) p105-15, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The 14;18 chromosome translocation, characteristic of most human follicular B-cell lymphomas, juxtaposes the **bcl-2** gene with the IgH locus, creating a **bcl-2**/IgH hybrid gene. By mechanisms that are still under investigation, this event increases the cellular levels of the **bcl-2** mRNA and thereby induces an overproduction of the antiapoptotic **BCL-2** protein which is likely responsible for neoplastic transformation. In an effort to identify potential upregulators of **bcl-2** activity in t(14;18) cells, we found, by strand-specific RT-PCR, a **bcl-2 antisense** transcript that is present in the t(14;18) DOHH2 and SU-DHL-4 but not in the t(14;18)-negative Raji and Jurkat lymphoid cell lines, and thus appears to be dependent on the **bcl-2**/IgH fusion. This **antisense** transcript is a hybrid bc1-2/IgH RNA, that originates in the IgH locus, encompasses the t(14;18) fusion site and spans at least the complete 3' UTR region of the **bcl-2** mRNA. To achieve some insight into its biological function, we treated the t(14;18) DOHH2 cell line with oligonucleotides (ODNs) by specifically targeting the bc1-2/IgH **antisense** strand. These ODNs lowered **bcl-2** gene expression, inhibited neoplastic cell growth by inducing apoptosis. We would like to propose the hypothesis that the bc1-2/IgH **antisense** transcript may contribute, by an unknown mechanism, to upregulation of **bcl-2** gene expression in t(14;18) cells. The possibility has been considered that the hybrid **antisense** transcript mask AU-rich motifs present in the 3' UTR of the **bcl-2** mRNA characterized in other genes as mRNA destabilizing elements.

3/3,AB/81 (Item 81 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08994425 97202454
Liposomal targeting of **bcl-2 antisense** oligonucleotides with enhanced stability into human myeloma cell lines.
Ollikainen H; Lappalainen K; Jaaskelainen I; Syrjanen S; Pulkki K
MediCity Research Laboratory, University of Turku, Finland.
Leukemia & lymphoma (SWITZERLAND) Dec **1996**, 24 (1-2) p165-74, ISSN 1042-8194 Journal Code: BNQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cationic liposomes improve the delivery of **antisense** oligonucleotides (ODNs) into cells. However, there is marked variability in the cellular uptake of ODNs into different cell lines. We used liposomes

containing dimethyloctadecylammonium bromide (DDAB) and dioleoylphosphatidylethanolamine (DOPE) to increase the delivery of phosphorothioester ODNs into four different myeloma cell lines. The delivery by cationic liposomes increased the delivery of **bcl-2** **antisense** ODNs by a factor of 9 to 45 as compared to plain ODNs. The stability of ODNs was increased with liposomes both in the culture medium and within the cells. Intact liposomal ODNs were detected inside the cells up to 24 hours with gel electrophoresis and phosphor imager analysis. **Antisense** ODNs had no effect on **bcl-2** mRNA levels. Also the proliferation of myeloma cells remained unchanged during the 3-day incubation period. Our study shows that liposomal **antisense** ODNs targeting **bcl-2** of human myeloma cells result in increased stability of ODNs with minimal toxicity. However, further modifications are needed to gain biological effects of **antisense** ODNs on human myeloma cells.

3/3,AB/82 (Item 82 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08985883 97182982
C-Myc and **Bcl-2** protein expression during the induction of apoptosis and differentiation in TNF alpha-treated HL-60 cells.
Kumakura S; Ishikura H; Tsumura H; Iwata Y; Endo J; Kobayashi S
Third Division of Internal Medicine, Shimane Medical University, Izumo, Japan.
Leukemia & lymphoma (SWITZERLAND) Oct **1996**, 23 (3-4) p383-94, ISSN 1042-8194 Journal Code: BNQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We examined c-Myc and **Bcl-2** protein expressions during the induction of apoptosis and differentiation in TNF alpha-treated HL-60 cells using a two-color flow cytometric method. We found that c-Myc protein was rapidly down-regulated in the apoptotic cells while **Bcl-2** protein was expressed at relatively high levels. Concomitantly with terminal differentiation **Bcl-2** protein was down-regulated in differentiating cells as well as c-Myc protein. We also showed that c-myc **antisense** oligonucleotides could induce apoptosis in HL-60 cells whereas **bcl-2** **antisense** did not induce apoptosis during the early time of treatment. These results suggest that the down-regulation of c-Myc protein expression is a primary event to induce apoptosis and neither consistent expression of c-Myc protein nor rapid down-regulation of **Bcl-2** protein is necessary for the initial processing of apoptosis in HL-60 cells. Furthermore, concomitant down-regulation of c-Myc and **Bcl-2** is closely associated with terminal differentiation and apoptotic cell death of HL-60 cells treated with TNF alpha.

3/3,AB/83 (Item 83 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08903847 97127457
Nerve growth factor rescues PC12 cells from apoptosis by increasing amount of **bcl-2**.
Katoh S; Mitsui Y; Kitani K; Suzuki T
Radioisotope Research Institute, Faculty of Medicine, University of Tokyo, Japan.
Biochemical and biophysical research communications (UNITED STATES) Dec 13 **1996**, 229 (2) p653-7, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Nerve growth factor (NGF) suppressed the decrease in number of viable PC12 cells after serum withdrawal from culture medium. Accordingly, the amount of **bcl-2**, a suppressive effector of apoptosis, increased

in these cells. **Bcl-2** **antisense** oligonucleotide suppressed not only the NGF-induced increase in **bcl-2** but also NGF-induced neuronal differentiation. Results of fluorescent DNA staining indicated that NGF inhibited the chromatin condensation of PC12 cells resulting from serum withdrawal and further that the **bcl-2** **antisense** oligonucleotide canceled this effect of NGF. The present results suggest that NGF rescues PC12 cells from apoptosis induced by serum withdrawal via up-regulation of **bcl-2**.

3/3,AB/84 (Item 84 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08880622 96259035
Antisense oligodeoxynucleotides to bax mRNA promote survival of rat sympathetic neurons in culture.
Gillardon F; Zimmermann M; Uhlmann E; Krajewski S; Reed JC; Klimaschewski L
II. Physiologisches Institut, Universitat Heidelberg, Germany.
Journal of neuroscience research (UNITED STATES) Mar 15 **1996**, 43 (6) p726-34, ISSN 0360-4012 Journal Code: KAC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous in vitro studies have shown that the presence of high levels of Bax protein accelerated the rate of cell death following growth factor deprivation and that the ratio of cell death repressor **Bcl-2** to cell death effector Bax may determine the susceptibility to apoptosis. Both **Bcl-2** and Bax protein expression has been detected in sympathetic neurons in vivo, and overexpression of **bcl-2** in cultured sympathetic neurons prevented apoptosis after deprivation of nerve growth factor (NGF). In the present study, we investigated the expression of bax and **bcl-2** in primary cultures of sympathetic neurons from rat superior cervical ganglia. Furthermore, we tested the effects of a partially phosphorothioated bax **antisense** oligodeoxynucleotide (ODN) on the survival of sympathetic neurons in cultures supplied with suboptimal concentrations of NGF (0.5 ng/ml). A constitutive expression of bax mRNA at high levels was detected by reverse transcription and polymerase chain reaction which did not change significantly following NGF reduction or treatment with bax **antisense** ODN. A decrease in **Bcl-2** immunoreactivity was observed by immunocytochemistry in tyrosine hydroxylase-positive neurons when cultured under suboptimal NGF concentrations, whereas **Bcl-2** immunolabeled non-neuronal cells were not affected. Maximal number of neurons was obtained in control cultures containing 50 ng/ml of NGF. Few neurons survived in cultures grown in 0.5 ng/ml of NGF for 2 days (12.0 +/- 1.5% of controls, mean +/- SEM). Addition of two control ODNs at 1 microM had no effect on neuronal survival (10.1 +/- 1.2% and 11.0 +/- 1.3%, respectively), while the number of neurons was significantly increased in NGF-reduced cultures treated with a bax **antisense** ODNs (1 microM) (31.5 +/- 1.9%). Administration of fluorescein-labeled ODNs demonstrated intracellular uptake into cultured neurons. Treatment with bax **antisense** ODNs caused a significant reduction of Bax protein levels in SCG neurons by 46 +/- 2.6% as assessed by immuno-cytochemistry and digital image analysis. Taken together, our data demonstrate a constitutive expression of bax mRNA in sympathetic neurons suggesting that activation of bax expression may not be required for neuronal cell death after NGF withdrawal. After changing to suboptimal NGF concentrations, the cell-specific reduction in **Bcl-2** immunoreactivity preceded morphological signs of degeneration indicating that growth factor starvation may down-regulate neuronal **bcl-2** expression. Treatment with bax **antisense** ODNs indicated that suppression of Bax protein synthesis may promote neuronal survival in the threshold situation of insufficient trophic support.

3/3,AB/85 (Item 85 [redacted]m file: 155)
DIALOG(R)File 155:MEDLI[redacted]R)

08862257 96368494
Induction of hepatoma cell apoptosis by c-myc requires zinc and occurs in the absence of DNA fragmentation.
Xu J; Xu Y; Nguyen Q; Novikoff PM; Czaja MJ
Department of Medicine, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
American journal of physiology (UNITED STATES) Jan **1996**, 270 (1 Pt 1) pG60-70, ISSN 0002-9513 Journal Code: 3U8
Contract/Grant No.: DK-44234, DK, NIDDK; CA-06576, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Since c-myc expression is increased during apoptosis in toxin-induced liver injury in vivo, the role of c-myc in liver cell apoptosis was investigated. The human hepatoma cell line HuH-7, which constitutively expresses c-myc, was stably transfected with sense and **antisense** c-myc expression vectors under the control of the zinc-inducible metallothionein promoter. None of the three cell types (wild-type, sense c-myc, or **antisense** c-myc) underwent apoptosis when cultured in serum-free medium (SFM). With the addition of SFM plus 37.5 microM zinc, wild-type and sense c-myc-expressing cells underwent rapid cell death, whereas **antisense** c-myc-expressing cells exhibited increased survival. This cell death had the light, fluorescent, and electron microscopic appearance of apoptosis, but did not result in DNA fragmentation. This apoptosis could be terminated by the addition of medium containing 2% fetal calf serum or the overexpression of **bcl-2** but not by supplementation with specific growth factors. Altering c-myc expression did not affect cellular metallothionein mRNA levels or the rate of cell death from copper or cadmium. The requirement for zinc and absence of DNA fragmentation in c-myc-induced hepatoma cell apoptosis under serum-free conditions provides further evidence of the complex regulation of apoptosis in different cell types.

3/3,AB/86 (Item 86 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08852055 97070436
Dopamine induces apoptotic cell death of a catecholaminergic cell line derived from the central nervous system.
Masserano JM; Gong L; Kulaga H; Baker I; Wyatt RJ
National Institute of Mental Health Neuroscience Center at Saint Elizabeths, Neuropsychiatry Branch, Washington, D.C. 20032, USA. masseraj@dirpc.nimh.nih.gov
Molecular pharmacology (UNITED STATES) Nov **1996**, 50 (5) p1309-15 , ISSN 0026-895X Journal Code: NGR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Dopamine produces a time- and dose-dependent increase in cell death in a clonal catecholaminergic cell line (CATH.a) derived from the central nervous system. Cell death also occurred after treatment with the catecholamines L-dihydroxyphenylalanine, norepinephrine, epinephrine, and isoproterenol, as well as the neurotoxic compound 6-hydroxydopamine. Cell death is not receptor mediated because selective noradrenergic and dopaminergic receptor agonists had no effect on CATH.a cell viability. Dopamine induces apoptotic cell death as indicated by DNA fragmentation measured by gel electrophoresis and by flow cytometric analysis. Apoptosis seems to be produced by dopamine autoxidation, because intracellular peroxides increase after dopamine treatment and cell death can be inhibited by catalase and N-acetylcysteine. N-acetylcysteine produced a dose-dependent decrease in dopamine-induced cell death; this correlated

with a decrease in per[redacted]e formation. In addition, **anti[redacted]se** to the antioxidant protein **bcl-2** increases the sensitivity of [redacted]TH.a cells to dopamine-induced cell death. These findings indicate that the oxidative products of dopamine cause neurotoxicity through apoptosis.

3/3,AB/87 (Item 87 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08837875 97050657
Parathyroid hormone-related peptide delays terminal differentiation of chondrocytes during endochondral bone development.
Lee K; Lanske B; Karaplis AC; Deeds JD; Kohno H; Nissenson RA; Kronenberg HM; Segre GV
Endocrine Unit, Massachusetts General Hospital, Boston 02114, USA.
Endocrinology (UNITED STATES) Nov **1996**, 137 (11) p5109-18, ISSN 0013-7227 Journal Code: EGZ
Contract/Grant No.: DK-47237, DK, NIDDK; DK-47038, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To test the hypothesis that PTH-related peptide (PTHrP) is a paracrine regulator of endochondral bone development, we localized PTHrP and its cognate receptor during normal skeletal development at both messenger RNA (mRNA) and protein levels and compared the growth plate phenotypes of PTHrP-deficient [(PTHrP(-/-)] mice to those of normal littermates [PTHrP(+/+]. PTHrP mRNA was expressed adjacent to uncavitated joints, in the perichondrium of long bones and to a lower level in proliferating chondrocytes. In contrast, PTHrP protein was most evident at the interface of proliferating and hypertrophic zones, where it colocalized with PTH/PTHrP receptor mRNA and protein. Most strikingly, the proliferating zone was dramatically shorter in PTHrP(-/-) cartilage, although the percentage of cells in S-phase of the cell cycle in the proliferating zone was indistinguishable between PTHrP(+/+) and PTHrP(-/-) mice. Terminal differentiation of chondrocytes, which was characterized by cell hypertrophy, apoptosis (DNA fragmentation and decreased **bcl-2** mRNA expression), and matrix mineralization, was more advanced in growth cartilage of PTHrP(-/-), compared with PTHrP(+/+) animals. These data demonstrate that PTHrP acts principally as a paracrine factor, which promotes elongation of endochondral bone by restraining or delaying the pace of chondrocytic development and terminal differentiation of growth-plate chondrocytes.

3/3,AB/88 (Item 88 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08797105 96437031
Interleukin-10 increases **Bcl-2** expression and survival in primary human CD34+ hematopoietic progenitor cells.
Weber-Nordt RM; Henschler R; Schott E; Wehinger J; Behringer D; Mertelsmann R; Finke J
Department of Hematology & Oncology, Albert-Ludwigs-University Medical Center, Freiburg, Germany.
Blood (UNITED STATES) Oct 1 **1996**, 88 (7) p2549-58, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Bcl-2 expression has been shown in hematopoietic progenitor cells. Through the use of **Bcl-2** specific **antisense** oligonucleotides we herein report the biologic importance of **Bcl-2** expression in primary human CD34+ hematopoietic progenitor cells committed to the myeloid lineage. In bone marrow or peripheral blood derived CD34+ cells **Bcl-2** specific **antisense** decreased

cell survival and inhibited the outgrowth of mixed myeloid colonies. A short-term overnight pretreatment of CD34+ cells with 25 mumol/L of **Bcl-2 antisense** in liquid culture completely ablated the growth of granulocyte-macrophage colony-forming cells (GM-CFC) in a subsequent 14 days methylcellulose colony assay. Control experiments using corresponding **Bcl-2** sense or nonsense oligonucleotides did not significantly impair cell survival or growth of GM-colony-forming unit. Western blot analyses revealed the **Bcl-2 antisense** dependent inhibition of expression of the **Bcl-2** protein in CD34+ progenitor cells. Furthermore, regulation of **Bcl-2** expression by various cytokines including interleukin-10 (IL-10) was studied. IL-10's effects on the formation of mixed myeloid colonies were examined in the absence or presence of **Bcl-2** specific **antisense**. In the absence of **Bcl-2 antisense** IL-10 significantly extended the colony forming potential of mixed myeloid colonies to 14 days. In the presence of **Bcl-2 antisense** rhIL-10 completely restored GM-CSF driven colony growth. Fluorescent microscopy, Western blot analysis, and reverse transcriptase-polymerase chain reaction revealed the IL-10 dependent increase in cellular expression of **Bcl-2** protein and **Bcl-2** mRNA transcripts in CD34+ cells. Thus these results show that **Bcl-2** expression is necessary for the formation of GM-CSF-dependent colony growth in vitro and that rhIL-10 increases **Bcl-2** expression and survival in primary human CD34+ hematopoietic progenitor cells that are committed to the myeloid lineage.

3/3,AB/89 (Item 89 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08795804 96424368

Down-regulation of **bcl-2** in AML blasts by all-trans retinoic acid and its relationship to CD34 antigen expression.

Bradbury DA; Aldington S; Zhu YM; Russell NH
Department of Haematology, Nottingham City Hospital.

British journal of haematology (ENGLAND) Sep **1996**, 94 (4) p671-5
, ISSN 0007-1048 Journal Code: AXC
Languages: ENGLISH
Document type: JOURNAL ARTICLE

High levels of expression of the **bcl-2** oncoprotein in acute myeloblastic leukaemia (AML) cells have been associated with low complete remission rates and poor survival. The sensitivity of AML blasts to drugs such as Ara-C can be increased by the down-regulation of **bcl-2** expression by **antisense** oligonucleotides. All-trans retinoic acid (ATRA) has been reported to increase the sensitivity of AML cell lines to Ara-C and to induce differentiation in the HL60 promyelocytic cell line, with both effects being accompanied by a decrease in **bcl-2** expression. Using flow cytometry and a monoclonal antibody to **bcl-2**, we have investigated the effects of ATRA (1 microM) on **bcl-2** expression in the blast cells of 25 AML patients and the K562 cell line after incubation for 72 or 24 h, respectively. Using Kolmogorov-Smirnov statistical analysis where a D value of > 0.12 was statistically significant, we found that in 8/25 AML samples and the K562 cells there was a significant decrease in **bcl-2** protein expression after incubation with ATRA (D value range 0.14-0.44). The mean peak fluorescence (MPF) values for the **bcl-2** levels of the ATRA responders (n = 8) was reduced to 35.5 +/- 6.9 following incubation with ATRA compared to 47.6 +/- 8.2 (mean +/- SEM) for control samples incubated in the absence of ATRA (P = 0.014). There was no significant difference between the baseline **bcl-2** molecules of equivalent soluble fluorochrome (MESF) levels in the ATRA responders (48.9 +/- 5.7, n = 8) and the non-responders (41.3 +/- 3.9, n = 17) (mean +/- SEM) (P = 0.28). The down-regulation of **bcl-2** expression by ATRA was particularly associated with CD34-negative AML and of the eight AML patients' cells that

responded to ATRA by down-regulating **bcl-2**, seven were CD34 negative ($P < 0.05$). Our data suggest that the addition of ATRA to combination chemotherapy would increase the chemosensitivity of some patients with AML, particularly CD34-negative AML, due to down-regulation of **bcl-2** expression.

3/3,AB/90 (Item 90 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08794070 96374107
Tumor-necrosis-factor-induced fibroblast growth factor-1 acts as a survival factor in a transformed endothelial cell line.
Maier JA; Morelli D; Menard S; Colnaghi MI; Balsari A
Department of Biomedical Sciences and Technologies, Ospedale San Raffaele, Milan, Italy.
American journal of pathology (UNITED STATES) Sep **1996**, 149 (3) p945-52, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Endothelial cells undergo apoptosis after withdrawal of growth factors, alterations in the extracellular matrix, or exposure to cytokines. Here we report that tumor necrosis factor (TNF)-alpha induces apoptosis of human endothelial cells derived from the umbilical vein in a dose-dependent fashion. Apoptosis is triggered through a pathway that is independent from the levels of **Bcl-2**. On the contrary, TNF stimulates the growth of spontaneously transformed human umbilical vein endothelial cells. This proliferative effect is mediated through the up-regulation of fibroblast growth factor-1 by TNF. The addition of specific fibroblast growth factor-1 **antisense** oligonucleotides inhibits TNF-induced fibroblast growth factor-1 expression, thus inhibiting the growth and triggering apoptosis of spontaneously transformed human umbilical vein endothelial cells.

3/3,AB/91 (Item 91 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08793574 96335809
Modulation of **bcl-2 antisense** RNA on programmed cell death of leukemic cell line]
Chen X; Wang W; Huang G
Department of Hematology, Xijing Hospital, Fourth Military Medical University, Xi'an.
Chung-hua i hsueh tsa chih (CHINA) Feb **1996**, 76 (2) p112-5, ISSN 0376-2491 Journal Code: CDG
Languages: CHINESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE ; English Abstract
OBJECTIVE: To investigate modulation of decrease of intrinsic **bcl-2** protein levels on programmed cell death of leukemia cells. METHOD: Gene transfection procedure was applied to observe the effect of **antisense** RNA-mediated suppression of **bcl-2** gene expression on programmed cell death of human T-lymphocytic leukemia cell line CEM. RESULTS: Temporary expression of **antisense bcl-2** gene could effectively reduce levels of intrinsic **bcl-2** protein of CEM cells and render it more sensitive to etoposide-induced cytotoxicity. Moreover, a great deal of apoptotic bodies and ladder DNA was always produced during etoposide-mediated killing of CEM and when CEM expressing **bcl-2 antisense** RNA served as target cells in particular, the amount of ladder DNA increased to around 40%. CONCLUSION: Programmed cell death is one of the mechanisms by which etoposide kills leukemic cells and is modulated by cellular intrinsic **bcl-2** protein.

3/3,AB/92 (Item 92 [redacted]m file: 155)
DIALOG(R)File 155:MEDLINE(R)

08793253 96319797
Induction of apoptosis in prostatic tumor cell line DU145 by staurosporine, a potent inhibitor of protein kinases.
Zhang H; Hoang T; Saeed B; Ng SC
Department 4MG, Aging and Degenerative Diseases Research, Abbott Laboratories, Abbott Park, Illinois 60064, USA.
Prostate (UNITED STATES) Aug **1996**, 29 (2) p69-76, ISSN 0270-4137 Journal Code: PB4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We are interested in studying the possibility of modulating prostatic cell growth by manipulating apoptosis. Here we show that 1 microM staurosporine (STS) induces a human androgen-independent prostatic tumor cell line, DU145, to undergo dramatic changes in morphology and results in programmed cell death. Several genes involved in apoptosis were analyzed for expression in STS-treated and untreated DU145 cells. It was observed that these genes were differentially regulated. The expression level of **bcl-2** , bcl-xL, Ich-1L remains unchanged in treated and untreated cells. On the other hand, DAD1 and interleukin-1 beta-converting enzyme (ICE) were downregulated while bcl-xs and Ich-1s were upregulated. By blocking **bcl-2** gene expression using **antisense** oligonucleotides, it was determined that the anti-**bcl-2** oligonucleotides have no effect on the proliferation of DU145 or STS-treated DU145 cells. These results demonstrate that programmed cell death can be induced in an androgen-independent prostatic cancer cell line and **BCL-2** was found not to play an important role in preventing STS-induced apoptosis in the DU145 cell line.

3/3,AB/93 (Item 93 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08709504 96210674
BCL2 regulates neural differentiation.
Zhang KZ; Westberg JA; Holtta E; Andersson LC
Department of Pathology, University of Helsinki, Haartman Institute, Finland.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 30 **1996**, 93 (9) p4504-8, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A main function attributed to the BCL2 protein is its ability to confer resistance against apoptosis. In addition to the constitutively high expression of BCL2, caused by gene rearrangement in follicular lymphomas, elevated expression of the BCL2 gene has been found in differentiating hematopoietic, neural, and epithelial tissues. To address the question of whether the expression of BCL2 is a cause or consequence of cell differentiation, we used a human neural-crest-derived tumor cell line, Paju, that undergoes spontaneous neural differentiation in vitro. The Paju cell line displays moderate expression of BCL2, the level of which increases in parallel with further neural differentiation induced by treatment with phorbol 12-myristate 13-acetate. Transfection of normal human BCL2 cDNA in sense and **antisense** orientations had a dramatic impact on the differentiation of the Paju cells. Overexpression of BCL2 cDNA induced extensive neurite outgrowth, even in low serum concentrations, together with an increased expression of neuron-specific enolase. Paju cells expressing the anti-sense BCL2 cDNA construct, which reduced the endogenous levels of BCL2, did not undergo spontaneous neural

differentiation. These cells acquired an epithelioid morphology and up-regulated the intermediate filament protein nestin, typically present in primitive neuroectodermal cells. The manipulated levels of BCL2 did not have appreciable impact on cell survival in normal culture. Our findings demonstrate that the BCL2 gene product participates in the regulation of neural differentiation.

3/3,AB/94 (Item 94 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08702112 96073234
Role of **Bcl-2** in the brain-derived neurotrophic factor survival response.
Allsopp TE; Kiselev S; Wyatt S; Davies AM
School of Biological and Medical Sciences, St Andrews University, Fife, UK.
European journal of neuroscience (ENGLAND) Jun 1 **1995**, 7 (6) p1266-72, ISSN 0953-816X Journal Code: BYG
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Developing neurons die if they fail to obtain an adequate supply of neurotrophins from their targets but how neurotrophins suppress cell death is not known. Although over-expression of exogenous **Bcl-2** can prevent the death of cultured neurons deprived of members of the nerve growth factor family of neurotrophins it is not known if this effect is physiologically relevant. To determine if **Bcl-2** participates in the neurotrophin survival response we used **antisense bcl-2** RNA to inhibit endogenous **Bcl-2** expression. Here we show that brain-derived neurotrophic factor (BDNF)-dependent neurons are killed by **antisense bcl-2** RNA in the presence of BDNF. However, when these neurons were supported with ciliary neurotrophic factor (CNTF) their survival was not affected by **antisense bcl-2** RNA. Likewise, the survival of CNTF-dependent ciliary neurons was not affected by **antisense bcl-2** RNA. Our findings suggest that **Bcl-2** is required for the BDNF survival response and that alternative, **Bcl-2** -independent survival mechanisms operate in sensory and parasympathetic neurons exposed to CNTF.

3/3,AB/95 (Item 95 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08699660 96028506
Role of p53 in leukemogenesis of chronic myeloid leukemia.
Lanza F; Bi S
Institute of Hematology, University of Ferrara, Italy.
Stem cells (UNITED STATES) Jul **1995**, 13 (4) p445-52, ISSN 1066-5099 Journal Code: BN2
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
This review attempts to provide current information on the role played by the p53 gene in normal and leukemic hematopoiesis with particular emphasis on chronic myeloid leukemia. On the basis of the currently available data we can argue that p53 acts as a negative regulator of proliferation of myeloid mature cells and CD34+ progenitors, and its action is mediated through changes in cell cycle kinetics, mainly before the S phase. The p53-dependent pathway is also regulated by several proteins, including p16, p21, p27 (cyclin-dependent kinase [CDK] inhibitors), and a few oncogenes (**bcl-2** , bax, MDM-2). Although there is some information about the changes in the p53 gene seen in various types of leukemia, the functions and biological importance of these changes in the pathogenesis of leukemia are still largely elusive. During the past several years,

accumulated evidence s[redacted]ests that changes in the p53 [redacted]ne are commonly associated with blast crisis of chronic myeloid leukemia (CML) but rarely with chronic phase, and they are represented by rearrangements, deletions and point mutations. As for most of the tumors, the majority of point mutations occur between exons 4 and 8 (hot regions). In patients with CML in blastic crisis the most frequent mechanism of p53 inactivation is complete deletion of one allele in association with a point mutation in the remaining allele.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/96 (Item 96 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08675190 94329554
The c-kit ligand suppresses apoptosis of human natural killer cells through the upregulation of **bcl-2**.
Carson WE; Haldar S; Baiocchi RA; Croce CM; Caligiuri MA
Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Aug 2 **1994**, 91 (16) p7553-7, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: CA39860, CA, NCI; CA01752, CA, NCI; CA09581, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The **bcl-2** protein plays a central role in the regulation of programmed cell death in a variety of tissues and is pivotal to the survival of lymphocytes in vivo. The growth factors responsible for survival of normal lymphocytes are unknown but are likely to maintain viability in part through the regulation of **bcl-2** expression. A subset of human natural killer (NK) cells (CD3-CD56bright) are unique among lymphocytes in their constitutive expression of c-kit, a tyrosine kinase cell surface receptor that binds c-kit ligand (KL). Alone, KL does not promote proliferation or further differentiation of CD56bright NK cells. We now report that, in the absence of serum or additional growth factors, KL prevents apoptosis of cultured CD56bright NK cells, as assessed by DNA fragmentation studies, and maintains viability, as measured by biologic responses (i.e., proliferation and cytotoxicity) to the subsequent addition of other cytokines. Furthermore, we demonstrate that KL induces CD56bright NK cells to express the **bcl-2** protein. In the presence of anti-c-kit antibody, the tyrosine kinase inhibitor genistein, or **bcl-2 antisense** oligonucleotide, the protective effect of KL on the survival of CD56bright NK cells is dramatically reduced. These data demonstrate that the binding of KL to its tyrosine kinase receptor results in the upregulation of **bcl-2**, thereby preventing apoptosis in this subset of normal human lymphocytes. As soluble KL is plentiful in normal human serum, this survival mechanism may be operative for CD56bright NK cells in vivo.

3/3,AB/97 (Item 97 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08661938 96180288
Bcl-2 inhibits retinoic acid-induced apoptosis during the neural differentiation of embryonal stem cells.
Okazawa H; Shimizu J; Kamei M; Imafuku I; Hamada H; Kanazawa I
Department of Neurology, Faculty of Medicine, University of Tokyo, Japan.
Journal of cell biology (UNITED STATES) Mar **1996**, 132 (5) p955-68, ISSN 0021-9525 Journal Code: HMV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We report here that all trans-retinoic acid (RA), a classical morphogen, induces apoptosis during the neural differentiation of the embryonic stem

cell line P19. The apoptotic cells showed, in addition to DNA cleavage, typical morphological changes including chromatin condensation, nuclear fragmentation, and cytoplasmic vacuolation. These apoptotic changes became obvious by 12 h after the addition of RA. The endogenous expression of **bcl-2** in surviving cells was down-regulated during this process, and the compelled expression of **bcl-2** by retroviral vectors reduced the number of apoptotic cells. Apoptosis was partially inhibited by adding **antisense** oligonucleotides against RA receptors (RARs) simultaneously or by transfecting a plasmid vector flanked with a RA-responsive element. **Antisense** oligonucleotides against retinoid X receptors (RXRs), the receptors for 9 cis-RA, did not inhibit apoptosis induced by all trans-RA. Cycloheximide and actinomycin D, inhibitors of protein and RNA syntheses, respectively, suppressed apoptosis. No changes were seen in the expression of tumor necrosis factors, their receptors, Fas, FasL, p53, or c-myc, molecules which have been suggested to participate in the apoptotic process. Addition of neurotrophins to the culture medium did not affect apoptosis. These findings suggest that the signals themselves, promote expression of molecules essential for apoptosis. Furthermore, we observed that RA induced apoptosis of cerebral neurons from murine embryos in primary culture, which suggests that RA might participate in cell death which occurs during neural development.

3/3,AB/98 (Item 98 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08659814 96224267
Arachidonate lipoxygenases as essential regulators of cell survival and apoptosis.
Tang DG; Chen YQ; Honn KV
Department of Radiation Oncology, Wayne State University, Detroit, MI 48202, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) May 28 **1996**, 93 (11) p5241-6, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: CA29997, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Arachidonic acid (AA) metabolites derived from both cyclooxygenase (COX) and lipoxygenase (LOX) pathways transduce a variety of signals related to cell growth. Here, we report that the AA LOX pathway also functions as a critical regulator of cell survival and apoptosis. Rat Walker 256 (W256) carcinosarcoma cells express 12-LOX and synthesize 12(S)- and 15(S)-hydroxyeicosatetraenoic acids as their major LOX metabolites. W256 cells transfected with 12-LOX-specific **antisense** oligonucleotide or **antisense** oligonucleotides directed to conserved regions of LOXs underwent time- and dose-dependent apoptosis. Likewise, treatment of W256 cells with various LOX but not COX inhibitors induced apoptotic cell death, which could be partially inhibited by exogenous 12(S)- or 15(S)-hydroxyeicosatetraenoic acids. The W256 cell apoptosis induced by **antisense** oligos and LOX inhibitors was followed by a rapid downregulation of **bcl-2** protein, a dramatic decrease in the **bcl-2**/bax ratio, and could be suppressed by **bcl-2** overexpression. In contrast, p53, which is wild type in W256 cells, did not undergo alterations during apoptosis induction. The results suggest that the LOX pathway plays an important physiological role in regulating apoptosis.

3/3,AB/99 (Item 99 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08659685 96220013

Oligonucleotides indu[redacted] apoptosis restricted to the t[redacted];18) DHL-4 cell line.

Morelli S; Alama A; Quattrone A; Gong L; Copreni E; Canti G; Nicolin A

Department of Pharmacology, University of Milan, Italy.

Anti-cancer drug design (ENGLAND) Jan **1996**, 11 (1) p1-14, ISSN 0266-9536 Journal Code: AC5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Most human follicular B-cell lymphomas are associated with t(14;18) chromosome translocation that joins the **bcl-2** gene with the IgH locus. This hybrid gene causes upregulation of **BCL-2** protein expression, endowing cells with survival advantage. Although early **BCL-2** overexpression is definitely responsible for immortalization/transformation, its exact role in the overt transformation as well as in the maintenance of the tumor phenotype is not known. The capacity of oligodeoxynucleotides (ODN) to modulate gene expression specifically has been exploited to downregulate the overexpression of **BCL-2** protein in the SU-DHL-4 human follicular B-cell lymphoma line by the use of sense ODN or **antisense** ODN or **antisense** ODN designed to encompass the unique nucleotide sequence in the fusion region of the hybrid transcript. The specific downregulation of the **bcl-2** transcript and of the relevant **BCL-2** protein in the treated cells activated programed cell death and inhibited growing cells. The antitumor activity was restricted to the DHL-4 cell line carrying the specific nucleotide sequence at the **bcl-2**/IgH joining region. Thus, DHL-4 lymphoma cells derived from the acute phase of human follicular B-cell lymphoma, although endowed with additional activated oncogenes, were growth inhibited by **bcl-2** downregulation with additional activated oncogenes, were growth inhibited by **bcl-2** downregulation in a genetically restricted fashion. The biological activity was exerted exclusively by ODNs synthesized in the sense orientation. The sense ODNs have been proposed to anneal the hybrid **bcl-2**/IgH **antisense** RNA as identified in this study.

3/3,AB/100 (Item 100 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08659006 96198032

Nerve growth factor rescues pigment cells from ultraviolet-induced apoptosis by upregulating **BCL-2** levels.

Zhai S; Yaar M; Doyle SM; Gilchrest BA

Department of Dermatology, Boston University of Medicine, MA 02118-2394, USA.

Experimental cell research (UNITED STATES) May 1 **1996**, 224 (2) p335-43, ISSN 0014-4827 Journal Code: EPB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Apoptosis plays an important role in eliminating dysfunctional damaged cells. For skin, the best characterized injurious environmental agent is ultraviolet (UV) irradiation. Most of the damaging UV irradiation is absorbed in the epidermis and leads to apoptosis of keratinocytes. However, epidermal melanocytes appear to be protected from UV-induced apoptosis. We now report that in pure cultures melanocytic cells undergo characteristic apoptosis after physiologic UV exposures. However, nerve growth factor (NGF) supplementation protects them from this programmed cell death. Furthermore, we show that NGF protects melanocytic cells from UV-induced apoptosis by upregulating **BCL-2** protein in these cells and that prior downregulation of **BCL-2** abrogates the NGF protective effect on melanocytes. Our data suggest that NGF, known to be constitutively produced by epidermal keratinocytes and induced in these cells after UV irradiation, may preserve the population of cutaneous melanocytes that would otherwise be depleted by casual sun exposure.

3/3,AB/101 (Item 10[redacted]rom file: 155)
DIALOG(R)File 155:MEDLINE(R)

08658637 96185047
Stromal cells regulate **bcl-2** and bax expression in pro-B cells.
Gibson LF; Piktel D; Narayanan R; Nunez G; Landreth KS
Department of Pediatrics, West Virginia University Health Sciences Center, Morgantown, USA.
Experimental hematology (UNITED STATES) Apr **1996**, 24 (5) p628-37
, ISSN 0301-472X Journal Code: EPR
Contract/Grant No.: AI23950, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
B lymphocyte production in the bone marrow depends on a cascade of regulatory cells and cytokines unique to the hematopoietic microenvironment. Fibroblastic stromal cells appear to be particularly important in regulating the earliest events in this lineage; however, it is still not clear whether the same or different sets of signals regulate maintenance of cell viability, proliferation, and differentiation of B lineage cells. In this study, we addressed the role of bone marrow stromal cells in survival and expansion of normal murine pro-B cells. Stromal cells were required for long-term proliferation of pro-B cell clone C1.92, and, in the presence of stromal cell line S10, pro-B cells expressed the proto-oncogene **bcl-2** . Removal of C1.92 cells from Stromal cell-derived signaling in support of pro-B cell viability. Due to its previously described role in regulating cell survival, we investigated whether stromal cells regulate **bcl-2** expression in pro-B cells. When removed from stromal cell cultures, pro-B cells rapidly lost **bcl-2** mRNA expression coincident with initiation of apoptosis. However, interruption of **bcl-2** expression with **antisense** oligonucleotides in the presence of stroma and interleukin-7 (IL-7) did not result in immediate cell death. Oligonucleotide-treated cells arrested in G(1) phase of the cell cycle 24 hours before the initiation of apoptosis. In contrast, removal of pro-B cells from stromal cell support resulted in rapid increase in BAX expression, correlating directly with initiation of apoptosis. These results suggest that **bcl-2** may, in part, regulate cell survival by interrupting the cascade of intracellular events that regulate cell cycle progression in lymphopoietic cells. Initiation of apoptosis in these cells appears to be more closely correlated with intracellular levels of BAX expression.

3/3,AB/102 (Item 102 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08658430 96180268
BCL2 oncogene protein expression in human hematopoietic precursors during fetal life.
Bonati A; Albertini R; Garau D; Pinelli S; Lunghi P; Almici C; Carlo-Stella C; Rizzoli V; Dall'Aglio P
Institute of Medical Pathology, Postgraduate Medical School of Clinical Immunology; University of Parma, Italy.
Experimental hematology (UNITED STATES) Feb **1996**, 24 (3) p459-65
, ISSN 0301-472X Journal Code: EPR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BCL2 proto-oncogene encodes a 25-kD protein that is characteristically localized in the inner mitochondrial membrane of the cell. It has been reported that BCL2 protein has the unique functional role of blocking programmed cells death without affecting proliferation. We have analyzed the expression of the BCL2 protein in fetal hematopoietic tissues from the

10th week of gestation age onward. Fetal thymus, liver and bone marrow and cord blood were investigated. The experiments were performed by the alkaline-antialkaline phosphatase (APAAP) technique by staining air-dried acetone-fixed cytospins and by dual-color immunofluorescent assay by staining mononuclear cell suspensions with monoclonal antibodies detecting BCL2 protein and antigens expressed by different hematopoietic subsets. Flow cytometric analyses were performed on FACSort's Comsort 32 (Becton Dickinson, San Jose, CA). The results have shown that the BCL2 protein is expressed in human fetal ontogenesis at the earliest stages examined. The major conceptual aspects of the results are 1) BCL2 is largely expressed in the hematopoietic cells during ontogenesis. BCL2+ cells include both immature and more differentiated subsets. Moreover, the 25-kD protein is expression in cell subsets well known to be high proliferating. This behavior suggests that BCL2 could have more complex functions than those previously described. 2) The expression in the major part of CD34+ cells suggests that BCL2 could play a role in stem cell survival. 3) BCL2 is expressed in not only medullary but also cortical thymocytes, where it could cooperate in positive selection processes. 4) The involvement of BCL2 in the immunosurveillance is indicated not only by its role in B and T cell lineages but also by its expression in particular subsets like that of the cytoplasmic CD3+ fetal liver NK cells. 5) The discrepancy observed between the results of transgenic mice analysis and in vitro inhibition experiments by **antisense** oligonucleotides performed for understanding BCL2 functions must stress the importance of the direct immunologic analysis of BCL2 in human hematopoietic cells.

3/3,AB/103 (Item 103 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08657597 96110800

Downregulation of Cu/Zn superoxide dismutase leads to cell death via the nitric oxide-peroxynitrite pathway.

Troy CM; Derossi D; Prochiantz A; Greene LA; Shelanski ML

Department of Pathology, Taub Center for Alzheimer's Disease Research, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.

Journal of neuroscience (UNITED STATES) Jan **1996**, 16 (1) p253-61
, ISSN 0270-6474 Journal Code: JDF

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We previously showed that the downregulation of Cu/Zn superoxide dismutase (SOD1) activity in PC12 cells by exposure to an appropriate **antisense** oligonucleotide causes their apoptotic death. In this report, we used this model to examine the pathways by which SOD1 downregulation leads to death and to compare these pathways with those responsible for death caused by withdrawal of trophic support. To improve delivery of the SOD1 **antisense** oligonucleotide, we coupled it to a carrier "vector" peptide homologous to the third helix of the Drosophila Antennapedia homeodomain. This caused not only efficient cellular uptake even in the presence of serum, but also inhibition of SOD1 activity and promotion of apoptosis at 100-fold lower concentrations of oligonucleotide. Death induced by SOD1 downregulation appeared to require the reaction of superoxide with nitric oxide (NO) to form peroxynitrite. In support of this, inhibitors of NO synthase, the enzyme responsible for NO synthesis, blocked death in our experiments, whereas NO generators and donors accelerated cell death. N-Acetylcysteine and chlorophenylthiol cAMP, which rescue PC12 cells and neurons from the withdrawal of nerve growth factor and other forms of trophic support, did not protect PC12 cells from SOD1 downregulation. In contrast, overexpression of **bcl-2**, which also rescues these cells form loss of trophic support, was equally effective in saving the cells in the SOD1 downregulation paradigm. Taken together with past findings, such observations suggest that SOD1 downregulation and withdrawal of trophic support trigger apoptosis via

distinct initial mechanisms but may utilize a common final pathway to bring about death. Our findings may be relevant to the causes and potential amelioration of neuronal degenerative disorders caused by impaired regulation of cellular levels of NO and superoxide.

3/3,AB/104 (Item 104 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08605023 95315059
Apoptosis in Pam212, an epidermal keratinocyte cell line: a possible role for **bcl-2** in epidermal differentiation.
Marthinuss J; Lawrence L; Seiberg M
Skin Biology Research Center, R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869, USA.
Cell growth & differentiation (UNITED STATES) Mar **1995**, 6 (3) p239-50, ISSN 1044-9523 Journal Code: AYH
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Programmed cell death is a controlled process that leads to the elimination of single cells via apoptosis, a mode of cell death with a characteristic morphology. During epidermal differentiation, keratinocytes migrate outward to become terminally differentiated cornified cells in a process involving programmed cell death pathway(s) and apoptosis. The molecular mechanisms regulating epidermal differentiation and apoptosis have not yet been elucidated. Here we show that a mouse keratinocyte cell line, Pam212, undergoes spontaneous apoptosis in culture. Apoptosis of Pam212 cells is demonstrated by both morphology and DNA oligonucleosomal degradation. The expression of **bcl-2**, a gene implicated in the negative control of apoptosis, was down-regulated in these cells by transfecting a **bcl-2-antisense** expression vector. The cells that down-regulate **bcl-2** expression exhibit enhanced apoptosis and further progress in the epidermal differentiation pathway. We analyzed the expression patterns of several genes that have been implicated in apoptosis in other systems. We show that the mRNA levels of c-myc, c-myb, c-fos, tumor necrosis factors (TNF) alpha and beta, TNF receptors I and II, interleukin 1 alpha, IFN-gamma, and transforming growth factor beta increase in the **antisense**-transfected cells. We suggest that **bcl-2** influences epidermal differentiation in Pam212 keratinocyte cells, and maybe in vivo, by negatively regulating several genes that are involved in apoptosis.

3/3,AB/105 (Item 105 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08602262 95129488
Inhibitors of oxidative stress mimic the ability of follicle-stimulating hormone to suppress apoptosis in cultured rat ovarian follicles.
Tilly JL; Tilly KI
Department of Population Dynamics, Johns Hopkins University, Baltimore, Maryland 21205-2179.
Endocrinology (UNITED STATES) Jan **1995**, 136 (1) p242-52, ISSN 0013-7227 Journal Code: EGZ
Contract/Grant No.: 5 P30 HD-06268-21, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have reported that members of the **bcl-2** gene family are expressed and gonadotropin regulated in ovarian granulosa cells during follicular maturation and atresia. Because **Bcl-2**, a protein that prevents apoptosis in several cell types, is reported to function as an antioxidant or free radical scavenger, the present studies were designed to investigate if oxidative stress plays a role in granulosa cell apoptosis

during follicular atresia in the immature rat ovary. In the first series of experiments, the role of oxidative stress in the induction of granulosa cell apoptosis was directly tested using a defined in vitro follicle culture system. Healthy antral follicles obtained from equine CG (eCG)-primed immature (27 day old) rats were incubated in serum-free medium for 24 h in the absence or presence of FSH (100 ng/ml; a control for inhibiting apoptosis), superoxide dismutase (SOD; 10-1000 U/ml), ascorbic acid (0.01-1 mM; a free radical scavenger), N-acetyl-L-cysteine (25-100 mM; a free radical scavenger and stimulator of endogenous glutathione peroxidase activity), or catalase (10-1000 U/ml). Granulosa cells within follicles incubated in medium alone exhibited extensive apoptosis after 24 h of incubation, and this onset of apoptosis was blocked by treatment with FSH (29 +/- 4% of controls; $P < 0.001$, $n = 3$). Moreover, apoptosis in follicles was also inhibited by treatment with SOD (44 +/- 4% of controls at 1000 U/ml; $P < 0.01$, $n = 3$), ascorbic acid (55 +/- 9% of controls at 1 mM; $P < 0.05$, $n = 3$), N-acetyl-L-cysteine (24 +/- 7% of controls at 100 mM; $P < 0.001$, $n = 3$), or catalase (35 +/- 6% of controls at 1000 U/ml; $P < 0.001$, $n = 3$). In the second series of experiments, complementary DNAs corresponding to secreted (SEC-SOD), copper/zinc-containing (Cu/Zn-SOD), and manganese-containing (Mn-SOD) forms of rat SOD, rat seleno-cysteine glutathione peroxidase (GSHPx), and rat catalase were isolated and used to synthesize **antisense** RNA probes for Northern and slot blot analysis of changes in SOD, GSHPx, and catalase gene expression during follicular maturation. In vivo priming of 25-day-old female rats for 2 days with 10 IU eCG, which promoted antral follicular growth and survival, increased levels of messenger RNA encoding SEC-SOD (216 +/- 9% of saline-treated controls, $P < 0.05$, $n = 3$) and Mn-SOD (222 +/- 14% of saline-treated controls, $P < 0.05$, $n = 3$) vs. saline-treated controls.(ABSTRACT TRUNCATED AT 400 WORDS)

3/3,AB/106 (Item 106 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08587274 96051283

Antisense oligodeoxyribonucleotide down-regulation of **bcl-2** gene expression inhibits growth of the low-grade non-Hodgkin's lymphoma cell line WSU-FSCCL.

Smith MR; Abubakr Y; Mohammad R; Xie T; Hamdan M; al-Katib A
Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.

Cancer gene therapy (UNITED STATES) Sep **1995**, 2 (3) p207-12, ISSN 0929-1903 Journal Code: CE3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The **BCL-2** gene product is involved in preventing apoptosis. The t(14,18) chromosomal translocation, which results in a fusion messenger RNA containing the entire coding region of **BCL-2** and a portion of the immunoglobulin heavy chain gene, is commonly found in follicular lymphoma and appears to play a role in lymphomagenesis by inhibiting cell death. We tested the hypothesis that downregulation of **BCL-2** would decrease accumulation of follicular lymphoma cells by treating the t(14,18)-carrying follicular lymphoma cell line WSU-FSCCL in vitro with **antisense** oligodeoxyribonucleotides (ODNs) directed against **BCL-2** . We found dose-dependent, sequence-specific inhibition of cell accumulation by an **antisense** unmodified ODN directed at codons 2 to 7, which downregulated **BCL-2** protein levels. This effect was near maximal at an ODN concentration of 40 micrograms/mL (6.9 mumol/L), with minimal toxicity by control sense, reverse, and mutated **antisense** ODN at the same concentration. The pre-B leukemia cell line REH showed no sequence-specific growth inhibition by the **antisense** ODN at these concentrations, and **BCL-2** protein levels were not altered. These data suggest that WSU-FSCCL may be useful in a murine model to optimize **antisense** ODN for potential therapeutic utility.

3/3,AB/107 (Item 10[redacted]rom file: 155)
DIALOG(R)File 155:MEDLINE(R)

08552901 96157357
Thymosin beta-10 accelerates apoptosis.
Hall AK
Department of Pharmacology, University of Cambridge, UK.
Cellular & molecular biology research (UNITED STATES) **1995**, 41 (3) p167-80, ISSN 0968-8773 Journal Code: BSK
Contract/Grant No.: CA-49422-03, CA, NCI; NIDDK 47-588-03
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The 5 Kd (MW), retinoic acid responsive thymosin beta-10 protein is expressed at relatively high levels in embryonic tissues, and its mRNA is abundant in a variety of tumors and tumor cell lines. Recently this protein (together with other members of the same protein family) was found to be a major intracellular G-actin binding protein. In the present study, plasmid-driven overexpression of thymosin beta-10 gene results in increased susceptibility of permanently transfected fibroblasts to undergo apoptosis. Conversely, knockout of the endogenous gene via overexpression of the **antisense** mRNA inhibited cell death induced by TNF-alpha and calcium ionophore A23187. Differential expression of thymosin beta-10 influenced cell proliferation, cell morphology, and expression/distribution of the antiapoptotic protein **bcl-2** . The presence of increased cytoplasmic thymosin beta-10 precipitated significant disruption of phalloidin-stained actin stress fibers while knockout of thymosin expression promoted F-actin assembly. These and other observations suggest that thymosin beta-10 (a) plays a significant and possibly obligatory role in cellular processes controlling apoptosis possibly by acting as an actin-mediated tumor suppressor, (b) perhaps functions as a neoapoptotic influence during embryogenesis, and (c) may mediate some of the pro-apoptotic anticancer actions of retinoids.

3/3,AB/108 (Item 108 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08551659 96110205
c-myc **antisense** oligodeoxyribonucleotides inhibit proliferation of non-small cell lung cancer.
Robinson LA; Smith LJ; Fontaine MP; Kay HD; Mountjoy CP; Pirruccello SJ
Division of Cardiovascular and Thoracic Surgery, University of South Florida, H. Lee Moffitt Cancer Center and Research Institute, Tampa 33612-9497, USA.
Annals of thoracic surgery (UNITED STATES) Dec **1995**, 60 (6) p1583-91, ISSN 0003-4975 Journal Code: 683
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: Mutation or deregulation of certain cellular genes (protooncogenes) results in expression of proteins that appear to promote malignant transformation. Human non-small cell lung cancer has been documented to express many such oncogenes including c-myc, **bcl-2**, and mutant p53. **Antisense** oligodeoxyribonucleotides (ASODN) complementary to these oncogenes were tested on three non-small cell lung cancer cell lines for their efficacy in inhibiting cellular proliferation and oncoprotein expression. METHODS: Established non-small cell lung cancer cell lines A427, SKMES-1, and A549 were grown in the presence of ASODNs complementary to messenger RNA of c-myc, **bcl-2** , p53, or controls at 1 mumol/L or 10 mumol/L concentrations for 4 or 10 days. Cellular proliferation was measured by tritiated thymidine uptake. Flow cytometry was used to quantitate oncoprotein expression. Intranuclear ASODN uptake was documented by fluoresceine-tagged ASODNs. RESULTS:

Fluoresceine-tagged ASODNs were readily taken up by all cell lines. c-myc, as well as **bcl-2** and p53 ASODNs, were found to inhibit proliferation of all cell lines significantly compared with controls, most notably in line A549 (40.1% +/- 7.1% of control, p = 0.000 with c-myc ASODN). **Antisense** c-myc reduced c-myc protein by as much as 71.3% in A427, although protein levels were only minimally reduced in the viable cells of the other lines. CONCLUSIONS: c-myc ASODNs inhibit proliferation of non-small cell lung cancer cell lines as well as reduce c-myc protein expression. **Antisense bcl-2** and p53 also cause similar growth inhibition. These results suggest a critical role for activation of these oncogenes in the growth of cultured lung cancer cells. Furthermore, the efficacy and rapid cellular uptake of ASODNs support the potential role of **antisense** targeting of oncogene expression for pharmacologic control of non-small cell lung cancer.

3/3,AB/109 (Item 109 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08550046 96068748
The human immunodeficiency virus type-1 Tat protein upregulates **Bcl-2** gene expression in Jurkat T-cell lines and primary peripheral blood mononuclear cells.
Zauli G; Gibellini D; Caputo A; Bassini A; Negrini M; Monne M; Mazzoni M; Capitani S
Institute of Human Anatomy, University of Ferrara, Italy.
Blood (UNITED STATES) Nov 15 **1995**, 86 (10) p3823-34, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The regulatory Tat protein of human immunodeficiency virus type-1 (HIV-1) exerts a pleyotropic activity on the survival and proliferation of different cell types in culture. In this report, we investigated the effect of either endogenous or exogenous Tat on **Bcl-2** proto-oncogene expression and cell survival in Jurkat T-cell lines and primary peripheral blood mononuclear cells. Stable and transient transfections of Jurkat cells with the cDNA of tat and a plasmid containing **Bcl-2** promoter in front of CAT (**Bcl-2** Pr/CAT) stimulated CAT activity and showed an increase of **Bcl-2** mRNA and protein expression. This effect was specifically related to tat, because Jurkat cells transfected with the cDNA of tat in **antisense** orientation, tat carrying a mutation in the amino acid cys22-gly22, or the control vector alone (pRPneo-SL3) did not show any significant difference in **Bcl-2** promoter activity with respect to parental Jurkat cells. We also observed a specific correlation between tat-induced **Bcl-2** gene expression and inhibition of apoptosis induced by serum withdrawal. Our results suggest that the structural integrity of the activation domain of Tat was required for the promotion of the **Bcl-2** promoter and Jurkat cell survival, because a single mutation in the aminoacid cys22 was sufficient to completely block the upregulation of **Bcl-2** and inhibition of apoptosis. Moreover, picomolar concentrations of native or recombinant Tat were able to upregulate **Bcl-2** expression both in Jurkat and primary peripheral blood mononuclear cells, suggesting that extracellular Tat, actively released by infected cells, may also play a significant role in suppressing apoptosis. An aberrant cell survival of lymphoid cells consequent to the upregulation of **Bcl-2** may represent an additional pathogenetic mechanism that could help explain both the dysregulated immune response and the frequent occurrence of hyperplastic/neoplastic disorders in HIV-1-seropositive individuals.

3/3,AB/110 (Item 110 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08550007 96067647
Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2.
Tsujii M; DuBois RN
Department of Medicine, Vanderbilt University Medical Center, Veterans Affairs Medical Center, Nashville, Tennessee 37232, USA.
Cell (UNITED STATES) Nov 3 **1995**, 83 (3) p493-501, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: DK47297-01A1, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Prostaglandin endoperoxide synthase 2, also referred to as cyclooxygenase 2 (COX-2), is a key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids. Rat intestinal epithelial (RIE) cells were permanently transfected with a COX-2 expression vector oriented in the sense (RIE-S) or **antisense** (RIE-AS) direction. The RIE-S cells expressed elevated COX-2 protein levels and demonstrated increased adhesion to extracellular matrix (ECM) proteins. E-cadherin was undetectable in RIE-S cells, but was elevated in parental RIE (RIE-P) and RIE-AS cells. RIE-S cells were resistant to butyrate-induced apoptosis, had elevated BCL2 protein expression, and reduced transforming growth factor beta 2 receptor levels. The phenotypic changes involving both increased adhesion to ECM and inhibition of apoptosis were reversed by sulindac sulfide (a COX inhibitor). These studies demonstrate that overexpression of COX-2 leads to phenotypic changes in intestinal epithelial cells that could enhance their tumorigenic potential.

3/3,AB/111 (Item 111 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08548949 96036039
The BCL2 major breakpoint region is a sequence- and cell-cycle-specific binding site of the Ku antigen.
DiCroce PA; Krontiris TG
Department of Medicine (Hematology/Oncology), Tufts University School of Medicine, Boston, MA, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 24 **1995**, 92 (22) p10137-41, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: CA51985, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The majority of translocations involving BCL2 are very narrowly targeted to three breakpoint clusters evenly spaced over a 100-bp region of the gene's terminal exon. We have recently shown that the immediate upstream boundary of this major breakpoint region (mbr) is a specific recognition site for single-strand DNA (ssDNA) binding proteins on the sense and **antisense** strands. The downstream flank of the mbr is a helicase binding site. In this report we demonstrate that the helicase and ssDNA binding proteins show reciprocal changes in binding activity over the cell cycle. The helicase is maximally active in G1 and early S phases; the ssDNA binding proteins are maximally active in late S and G2/M phases. An inhibitor of helicase binding appears in late S and G2/M. Finally, at least one component of the helicase binding complex is the Ku antigen. Thus, a protein with helicase activity implicated in repair of double-strand breaks, variable (diversity) joining recombination, and, potentially, cell-cycle regulation is targeted to the BCL2 mbr.

3/3,AB/112 (Item 112 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08547220 95399283

BCL-2 expression by leukaemic blasts in a SCID mouse model of biphenotypic leukaemia associated with the t(4;11)(q21;q23) translocation.

Pocock CF; Malone M; Booth M; Evans M; Morgan G; Greil J; Cotter FE
ICRF Oncology Group, Institute of Child Health, London.

British journal of haematology (ENGLAND) Aug **1995**, 90 (4) p855-67, ISSN 0007-1048 Journal Code: AXC
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Acute leukaemia of infancy is associated with abnormalities at chromosome band 11q23, and has a poor prognosis. The gene involved. Mixed Lineage Leukaemia (MLL), has been identified and has the characteristics of a transcription factor. The **BCL-2** gene responsible for blocking of programmed cell death is highly expressed in a number of haematological malignancies, both with and without the t(14;18) translocation. Those without the translocation include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL). In these diseases the **BCL-2** protein is implicated in drug resistance to apoptosis-inducing chemotherapeutic agents. High **BCL-2** expression is also associated with autonomous growth of leukaemic blasts in culture and predicts a poor prognosis. The SEM cell line, established using blood lymphoblasts from a 5-year-old girl in first relapse with t(4;11) ALL, expresses lymphoid (CD19) and myeloid (CD13) cell surface markers. In cell culture, a subpopulation of cells (< 30%) express the **BCL-2** protein. A reproducible model of true biphenotypic leukaemia in the SCID mouse has been established using the SEM-K2 cell line (a subclone of the SEM cell line). Between 5 and 50 million cells injected intravenously (i.v.) produce complete replacement of the murine bone marrow by day 30, associated with blood lymphoblastosis and infiltration of the spleen. No tumour masses were seen. Fluorescence in situ hybridization (FISH) analysis of the cell line and blood from the SCID-human (SCID-hu) chimaera has confirmed the presence of the t(4;11). Reverse transcriptional-polymerase chain reaction (RT-PCR) reveals that the breakpoint lies between exons 7 and 8 of the MLL-1 gene on chromosome 11 (the main breakpoint region). A further translocation, t(7;13), has been identified. Fluorescent antibody cell sorter (FACS) analysis of tumour material recovered from the SCID-hu model confirms expression of CD19 and CD13 identical to that of the cell line. In addition, **BCL-2** expression in SCID-hu marrow is now seen in the majority of tumour cells. **BCL-2** expression appears to confer a survival advantage to the blast cells in vivo. This reproducible model of biphenotypic leukaemia suggests that **BCL-2** expression may play a role in leukaemogenesis. The model is suitable for the investigation of gene-targeted therapy, including **antisense** oligonucleotides, directed towards the MLL and **BCL-2** genes.

3/3,AB/113 (Item 113 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08546117 95368651

Estrogen promotes chemotherapeutic drug resistance by a mechanism involving **Bcl-2** proto-oncogene expression in human breast cancer cells.

Teixeira C; Reed JC; Pratt MA
Department of Pharmacology, University of Ottawa, Ontario, Canada.

Cancer research (UNITED STATES) Sep 1 **1995**, 55 (17) p3902-7, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Recent studies have shown that the **Bcl-2** protein suppresses programmed cell death or apoptosis induced by a variety of stimuli including chemotherapeutic drugs. Because estrogen promotes the survival of

estrogen-dependent breast cancer cells in vivo, we investigated whether estrogen might regulate levels of **Bcl-2** gene expression in an estrogen-responsive human breast cancer cell line. Estrogen receptor-positive MCF-7 human breast cancer cells cultured in the presence of estrogen express the 8.5-kb **Bcl-2** mRNA transcript. Depletion of estrogen from the medium results in loss of expression of the mRNA, whereas reexposure to estrogen markedly induces the **Bcl-2** transcript. The changes in **Bcl-2** mRNA are paralleled by changes in **Bcl-2** protein levels. Estrogen-induced increases in **Bcl-2** are significantly inhibited by inclusion of the pure antiestrogen ICI 164,384 in the medium. The Bax protein that heterodimerizes with **Bcl-2** and promotes cell death is expressed in MCF-7 cells grown in the presence of estrogen and is unaffected by culture in estrogen-free medium. Estrogen depletion doubles the sensitivity of MCF-7 cells to the cytotoxic effects of Adriamycin compared with cells cultured in medium supplemented with estrogen, consistent with a decrease in the **Bcl-2** levels. MCF-7 cells treated simultaneously with estrogen and ICI 164,384 exhibit markedly lower resistance to Adriamycin compared with cells treated with estrogen alone. In the absence of estrogen, MCF-7 cells transfected with **Bcl-2** expression plasmids display a marked increase in resistance to Adriamycin. In the presence of estrogen, MCF-7 cells expressing **Bcl-2** **antisense** transcripts are rendered twice as sensitive to acute Adriamycin cytotoxicity as a control clone. We conclude that estrogen can promote resistance of estrogen receptor bearing human breast cancer cells to chemotherapeutic drugs through a mechanism that involves regulation of the **Bcl-2** proto-oncogene.

3/3,AB/114 (Item 114 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08544081 95315480
The role of **Bcl-2** protein and autocrine growth factors in a human follicular lymphoma-derived B cell line.
Blagosklonny MV; Neckers LM
Clinical Pharmacology Branch, National Cancer Institute, National Institute of Health, Bethesda, MD 20892, USA.
European cytokine network (FRANCE) Jan-Feb **1995**, 6 (1) p21-7,
ISSN 1148-5493 Journal Code: A56
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have shown that the ability of the human follicular lymphoma-derived cell line SU-DHL-6 to proliferate and survive in vitro depends on both **Bcl-2** expression and multiple autocrine growth factors. Treatment with **Bcl-2** **antisense** (AS **Bcl-2**) decreased **Bcl-2** protein levels. However, a cytotoxic effect was seen only at very restricted cell densities. Below such densities cells underwent spontaneous death without any treatment, while above these cell densities no cytotoxic effect of AS **Bcl-2** could be seen. The conditioned medium of SU-DHL cells supported the survival and growth of these cells cultivated at low cell densities and partially reversed the cytotoxicity associated with **Bcl-2** depletion. RT/PCR analysis revealed autocrine expression of IL-1 beta, IL-2, IL-5 and TNF-beta in SU-DHL cells. Neutralizing antibodies against these cytokines inhibited SU-DHL proliferation. Thus, development of autocrine GF secretion may be the second step in the pathogenesis of follicular lymphomas.

3/3,AB/115 (Item 115 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08540521 95204963

A simple assay for exa[redacted]ing the effect of transiently [redacted]pressed genes on programmed cell death.

Memon SA; Petrak D; Moreno MB; Zacharchuk CM

Laboratory of Immune Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1152.

Journal of immunological methods (NETHERLANDS) Mar 13 **1995**, 180 (1) p15-24, ISSN 0022-1759 Journal Code: IFE

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Programmed cell death (PCD) has been observed in a wide variety of cell types in response to physiologic signals or types of stress. How these stimuli trigger PCD, and whether there is a common PCD signal transduction pathway, is not clear. As more genes are described that may participate in or regulate PCD, an assay system in which gene products can easily be introduced and/or modulated would be of great value. To avoid the generation and screening of multiple individual stable cell transfectants, a simple transient transfection death assay has been developed. 2B4.11, a murine T cell hybridoma, was transfected by electroporation with a constitutively active beta-galactosidase reporter gene and the cells were incubated in culture medium or with a PCD-inducing stimulus. The amount of beta-galactosidase activity remaining in the intact cells at the end of the culture period represented only viable transfected cells. **Bcl-2** was chosen to examine whether this system would be useful to study the effect of transiently transfected genes since it blocks PCD in a number of experimental systems. Consistent with data obtained using stable transfectants, transient expression of **Bcl-2** in 2B4.11 completely protected cells from glucocorticoid- and cytotoxic agent-induced PCD. This protection from death was confirmed at the individual cell level by the transient co-expression of a class I Ld surface antigen and flow cytometric analysis. Some of the advantages of the transient transfection death assay described here are; (1) the simple and sensitive beta-galactosidase assay, (2) the rapidity of the assay, (3) the ability to perform conventional viability assays to monitor treatment-induced cytotoxicity, (4) multiple gene products can be tested alone, and in combination, (5) **antisense** or dominant negative approaches can be used, and (6) the adaptability of this assay system to other cell types, transfection techniques, or reporter and expression vectors. The transient transfection death assay should make it easier to identify and order important steps in the PCD signal transduction pathways.

3/3,AB/116 (Item 116 from file: 155)

08539590 95153658

Androgens induce resistance to **bcl-2**-mediated apoptosis in LNCaP prostate cancer cells.

Berchem GJ; Bosseler M; Sugars LY; Voeller HJ; Zeitlin S; Gelmann EP

Department of Medicine, Lombardi Cancer Center, Georgetown University School of Medicine, Washington, DC 20007.

Cancer research (UNITED STATES) Feb 15 **1995**, 55 (4) p735-8, ISSN 0008-5472 Journal Code: CNF

Contract/Grant No.: CA57176, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We describe an in vitro model for prostate cancer treatment that suggests a potential benefit for combined androgen ablation and cytotoxic chemotherapy. Androgen treatment of the LNCaP hormone-dependent human prostate cancer cell line induces increased expression of the **BCL-2** protein. Increased levels of this protein are known to mediate inhibition of apoptosis. LNCaP cells, however, did not undergo apoptosis in response to androgen withdrawal. Etoposide exerts its cytotoxicity on LNCaP and other cells by inducing apoptosis. In vitro etoposide cytotoxicity was diminished 83% in the presence of either 10(-8) M dihydrotestosterone or

10(-9) M R1881 in LNCaP cells. The interaction between androgen and etoposide was mediated through the **BCL-2** protein, since **bcl-2 antisense** oligonucleotides blocked the protective effect of androgens on etoposide cytotoxicity.

3/3,AB/117 (Item 117 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08539523 95147474
Inhibition of **bcl-2** with **antisense** oligonucleotides induces apoptosis and increases the sensitivity of AML blasts to Ara-C.
Keith FJ; Bradbury DA; Zhu YM; Russell NH
Department of Haematology, Nottingham City Hospital, UK.
Leukemia (ENGLAND) Jan **1995**, 9 (1) p131-8, ISSN 0887-6924 Journal Code: LEU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have previously shown that blasts from acute myeloid leukaemia (AML) patients which grow autonomously in culture have high **bcl-2** expression which in turn has been linked to a poor clinical response to chemotherapy. The **bcl-2** protein promotes cell survival by preventing the onset of apoptosis or programmed cell death following growth-factor deprivation. **Bcl-2** has also been shown to be responsible for chemo-resistance in human leukaemic cell lines. Here we have investigated the role of **bcl-2** expression in mediating resistance to apoptosis induced by cytosine arabinoside in vitro. The blasts from 17 AML patients exhibiting autonomous growth in a blast cell colony assay and expressing high levels of **bcl-2** protein were studied. Incubation of the blasts with **antisense** oligonucleotides directed against **bcl-2** mRNA resulted in a significant decrease in expression of the **bcl-2** protein in seven of the 17 samples. In these seven cases the decreased expression of **bcl-2** was accompanied by increased apoptosis and the susceptibility of the blasts to apoptosis induced by Ara-C was increased in the presence of **bcl-2 antisense**. As a high level of **bcl-2** defines a group of AML patients who exhibit a poor response to chemotherapy, the demonstration that chemosensitivity of a significant proportion of these patients can be increased by **bcl-2 antisense** suggests this approach may have clinical potential.

3/3,AB/118 (Item 118 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08461308 96091139
mel-18, a Polycomb group-related mammalian gene, encodes a transcriptional negative regulator with tumor suppressive activity.
Kanno M; Hasegawa M; Ishida A; Isono K; Taniguchi M
Division of Molecular Immunology, School of Medicine, Chiba University, Japan.
EMBO journal (ENGLAND) Nov 15 **1995**, 14 (22) p5672-8, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The mammalian mel-18/bmi-1 gene products share an amino acid sequence and a secondary structure, including a RING-finger motif, with the Drosophila Polycomb group (PcG) gene products Psc and Su(z)2, implying that they represent a gene family with related functions. As Drosophila PcG gene products are thought to function as transcriptional repressors by modifying chromatin structure, Mel-18/Bmi-1 might be expected to have similar activities. Here we have analyzed the function of mel-18 and found that Mel-18 acts as a transcriptional repressor via its target DNA sequence,

5'-GACTNGACT-3'. Interestingly, this binding sequence is found within regulatory or non-coding regions of various genes, including the c-myc, **bcl-2** and Hox genes, suggesting diverse functions of mel-18 as the mammalian homolog of the PcG gene. We also demonstrate that mel-18 has tumor suppressor activity, in contrast to bmi-1, which has been defined as a proto-oncogene.

3/3,AB/119 (Item 119 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08408698 96003408
Induction of bcl-x by CD40 engagement rescues sIg-induced apoptosis in murine B cells.
Wang Z; Karras JG; Howard RG; Rothstein TL
Department of Medicine, Boston University Medical Center, MA 02118, USA.
Journal of immunology (UNITED STATES) Oct 15 **1995**, 155 (8) p3722-5, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI29690, AI, NIAID; T32-AI07309, AI, NIAID; T32-CA64070-01, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CD40L, a membrane protein of activated T cells, interacts with the B cell receptor CD40. This interaction has been implicated in the rescue of germinal center B cells from apoptosis and in the rescue of WEHI-231 B lymphoma cells from sIg-induced apoptosis. In this report, we have demonstrated that the signal mediated by CD40L acts upon bcl-x, a **bcl-2** homologue. bcl-x expression is strongly enhanced by CD40 receptor engagement, while there is little or no induction by sIg cross-linking. The expression of bax and **bcl-2** is not significantly affected by either CD40L or sIg cross-linking. **Antisense** but not sense phosphorothioate oligonucleotide for bcl-x can partially block this CD40-mediated apoptotic rescue. This result suggests that the up-regulation of bcl-x by CD40L plays an important role in CD40-mediated apoptotic rescue in murine B cells.

3/3,AB/120 (Item 120 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08396731 95403471
Regulation of the Fas apoptotic cell death pathway by Abl.
McGahon AJ; Nishioka WK; Martin SJ; Mahboubi A; Cotter TG; Green DR
Division of Cellular Immunology, La Jolla Institute for Allergy and Immunology, California 92037, USA.
Journal of biological chemistry (UNITED STATES) Sep 22 **1995**, 270 (38) p22625-31, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Relatively little is known about oncogene involvement in the regulation of Fas-mediated apoptosis. Inhibition of Fas-induced cell death by the **bcl-2** oncogene has been demonstrated to be only partial. In light of a growing body of evidence for the Abl kinase as a negative regulator of cell death, we sought to determine whether Abl expression could protect against Fas-mediated cell death. To address this question, we utilized two separate strategies. In the first, we expressed human Fas in K562, a chronic myelogenous leukemia cell line, which constitutively expresses bcr-abl and examined the effects of Fas ligation in these cells. Fas-positive K562 transformants (K562.Fas) were found to be protected against Fas-mediated cell death. However, down-regulation of Bcr-Abl protein levels in K562.Fas cells using **antisense** oligonucleotides targeted to bcr-abl mRNA rendered these cells highly susceptible to Fas-induced death. In the second approach we utilized a Fas-positive HL-60

cell line, which we [redacted]nsfected with a temperature-s[redacted]sitive mutant of v-Abl. HL-60.v-Ablts [redacted]nsfectants were found to b[redacted] protected from Fas-induced apoptosis at the permissive but not the restrictive temperature for the Abl kinase. Taken together, these observations identify the Abl kinase as a negative regulator of Fas-mediated cell death. Since Abl was also found to block apoptosis mediated by ceramide, a recently proposed downstream effector of the apoptotic pathway initiated by Fas, we propose that Abl exerts its protective effects downstream of the early Fas-initiated signaling events.

3/3,AB/121 (Item 121 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08308825 95293939
Expression of differentiation-related phenotypes and apoptosis are independently regulated during myeloid cell differentiation.
Terui Y; Furukawa Y; Sakoe K; Ohta M; Saito M
Division of Hemopoiesis, Institute of Hematology, Jichi Medical School, Tochigi.
Journal of biochemistry (JAPAN) Jan **1995**, 117 (1) p77-84, ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
When human promyelocytic leukemia cell line HL-60 was treated with various differentiation-inducers, apoptosis always occurred after the full appearance of differentiation-related phenotypes. However, the two phenomena could be dissociated when HL-60 cells were treated with PDBu. When HL-60 cells were cultured with PDBu for more than 36 h, apoptosis was induced following differentiation. Apoptosis was not, however, observed when PDBu was removed within 24 h, even though induction of differentiation-related phenotypes, such as NBT-reducing ability and surface marker expression, was the same as that in the control. Northern blot analysis revealed that **bcl-2** mRNA was rapidly down-regulated within 6 h of the treatment with PDBu. The amount of **bcl-2** mRNA recovered to that of undifferentiated HL-60 cells when PDBu was washed out within 24 h. In contrast, the recovery of **bcl-2** was incomplete when the cells were treated with PDBu for more than 36 h, suggesting that **bcl-2** is also a critical regulator of the cell fate during myeloid differentiation. This hypothesis was confirmed by experiments using **antisense** oligonucleotides, i.e., blocking the recovery of **bcl-2** mRNA by **antisense** oligonucleotides could result in the induction of apoptosis in HL-60 cells from which PDBu was removed within 24 h. Moreover, overexpression of **BCL-2** in HL-60 cells could block apoptosis during differentiation without any significant effect on differentiation itself. These results strongly suggest that apoptosis is not a simple consequence of differentiation-induction, and that apoptosis and differentiation are regulated independently in myeloid cells.

3/3,AB/122 (Item 122 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08228307 94341744
Meeting report: **antisense** oligonucleotides.
Martinelli G; Ferrari S
Istituto di Ematologia L.e A. Seragnoli, Universita di Bologna, Italy.
Haematologica (ITALY) Mar-Apr **1994**, 79 (2) p184-8, ISSN 0390-6078 Journal Code: FYB
Languages: ENGLISH
Document type: CONGRESSES
The use of **antisense** oligonucleotides as a therapeutic tool in

modulating gene expression represents a newly established strategy for treating diseases. Such oligomers may be designed to complement a region of a specific gene or messenger RNA. Using this approach, oligonucleotides can serve as a potential block of transcription or translation through sequence-specific hybridization with targeted genetic segments. In the Fourth Meeting of the Italian Society of Experimental Hematology "Discutiamone Insieme", authors reported the use of in vitro synthesized oligonucleotides to inhibit normal and chimeric gene expression of **bcl-2** in normal and neoplastic cell lines, respectively, that carry the t(14;18) translocation. The roles of c-myb and B-myb in the control of the proliferation and differentiation of normal hematopoietic cell lines have been investigated by selective inhibition of the expression of specific transcripts. To get some insight into the correlation between proliferation and differentiation in myeloid cells, some authors studied and reported the differentiation potential of G1-arrested cells obtained by a specific oligodeoxynucleotide complementary to the 5' region of the c-myb mRNA. The use of anti-P53 **antisense** oligos in the modulation of the growth of normal and neoplastic bone marrow progenitors was presented and confirmed the pivotal role of this gene in cell cycle control. The role of abl gene expression in normal and chronic myelogenous leukemia (CML) cells is not yet completely understood. Selective inhibition of this proto-oncogene and of the abl-bcr oncogene have been achieved by using of c-abl sequence specific **antisense** oligonucleotides; this approach sheds new light on the function of this gene in CML.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/123 (Item 123 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08210233 94358414
Involvement of LFA-1/intracellular adhesion molecule-1-dependent cell adhesion in CD40-mediated inhibition of human B lymphoma cell death induced by surface IgM crosslinking.
Sumimoto S; Heike T; Kanazashi S; Shintaku N; Jung EY; Hata D; Katamura K ; Mayumi M
Department of Pediatrics, Faculty of Medicine, Kyoto University, Japan.
Journal of immunology (UNITED STATES) Sep 15 **1994**, 153 (6) p2488-96, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
B cells have been shown to receive negative signals for their growth through crosslinking of surface IgM (sIgM), and it has been demonstrated that anti-IgM Abs induce B cell death. Proliferation of B cells in response to Ag stimulation in vivo may thus require additional signals that inhibit the sIgM-transduced negative signals. Signaling through CD40 has been proposed as a candidate for such costimulatory signals. To investigate the role of CD40-transduced signals in sIgM-mediated B cell death, we used a human B cell line (DND-39) that expresses sIgM, sIgD, and CD40. Crosslinking of sIgM, but not sIgD, by Abs induced DND-39 cell death. The dying cells showed the morphology of apoptosis and DNA fragmentation. Anti-CD40 Abs induced homotypic adhesion of DND-39 cells and rescued them from anti-IgM Ab-induced cell death. Anti-CD40 Abs inhibited anti-IgM Ab-induced cell death when added within 3 h after stimulation with anti-IgM Ab. Treatment with Abs against CD11a, CD18, or CD54 inhibited not only the homotypic adhesion but also the inhibition of anti-IgM Ab-induced apoptosis by anti-CD40 Ab. CD11a **antisense** decreased the surface CD11a expression, the anti-CD40 Ab-induced homotypic adhesion, and the inhibitory effect of anti-CD40 Ab on anti-IgM Ab-induced apoptosis. The data show that LFA-1/ICAM-1-dependent cell adhesion induced by signaling through CD40 plays an important role in the inhibition of anti-IgM Ab-induced apoptosis of DND-39 cells.

3/3,AB/124 (Item 124 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08201735 94226946
Regulation of chemoresistance by the **bcl-2** oncoprotein in non-Hodgkin's lymphoma and lymphocytic leukemia cell lines.
Reed JC; Kitada S; Takayama S; Miyashita T
La Jolla Cancer Research Foundation, Cancer Research Center, California.
Annals of oncology (NETHERLANDS) **1994**, 5 Suppl 1 p61-5, ISSN 0923-7534 Journal Code: AYF
Contract/Grant No.: CA-47956, CA, NCI; CA-60381, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: The **bcl-2** gene becomes activated by 14;18 chromosomal translocations in the majority of low-grade non-Hodgkin's lymphomas (NHLs) and is expressed at high levels in the absence of gene rearrangements in a high proportion of B-cell chronic lymphocytic leukemias (B-CLLs). The protein encoded by **bcl-2** contributes to neoplastic cell expansion by prolonging cell survival through its ability to block programmed cell death (apoptosis). Because many chemotherapeutic drugs have been shown ultimately to kill tumor cells through mechanisms consistent with programmed cell death, we tested whether the relative levels of **bcl-2** oncoprotein influence the sensitivity of lymphoma and leukemia cell lines to killing by conventional cytotoxic drugs commonly used in the treatment of cancer. METHODS: Leukemia cell lines with low levels of **bcl-2** expression were stably infected with recombinant **bcl-2** retroviruses to achieve elevations in **bcl-2** protein levels. Lymphoma cell lines with high levels of **bcl-2** expression as the result of 14;18 translocations were either stably transfected with inducible **bcl-2 antisense** expression plasmids or treated with **bcl-2 antisense** oligonucleotides to achieve reductions in **bcl-2** protein levels. The sensitivity of these genetically modified cells to killing by various antineoplastic drugs was then determined. RESULTS: Gene transfer-mediated elevations in **bcl-2** protein levels in lymphocytic leukemia cell lines was correlated with markedly elevated resistance to killing by all cytotoxic drugs tested. Conversely, **antisense**-mediated reductions in **bcl-2** protein levels in t(14;18)-containing NHL cell lines resulted in enhanced sensitivity to all anticancer drugs. CONCLUSIONS: The relative levels of **bcl-2** oncoprotein represent one of the key determinants of the sensitivity of lymphocytic cells to killing by essentially all drugs currently available for the treatment of cancer.

3/3,AB/125 (Item 125 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08191645 95126512
Anticancer drug resistance and inhibition of apoptosis.
Desoize B
GIBSA, Institut Godinot, Reims, France.
Anticancer research (GREECE) Nov-Dec **1994**, 14 (6A) p2291-4, ISSN 0250-7005 Journal Code: 59L
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Apoptosis is a new concept which could be of great importance in the understanding and treatment of cancer. An important feature is the discovery of inhibitors of apoptosis, because they induce resistance to chemotherapeutic drugs and irradiation. **Bcl-2** is the most well known of these apoptosis inhibitors. When it is overexpressed cells are less sensitive to cytotoxic drugs; on the contrary, when it is underexpressed they are more sensitive. Clinically, **bcl-2**

expression is associated with a poor prognosis in several cancers. **Bcl-2** protein, p26-**bcl**[redacted] is located in the outer mitochondrial membrane, the nuclear envelope and the smooth endoplasmic reticulum. P26-**bcl-2** is an antioxidant; this property could explain the anti-apoptotic activity since peroxides seem to be important mediators of apoptosis. **Bcl-2 antisense** oligonucleotides are able to reverse the apoptosis inhibition. New cancer treatments should take into account the expression of **bcl-2**.

3/3,AB/126 (Item 126 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08191132 95108079
A role for deregulated c-Myc expression in apoptosis of Epstein-Barr virus-immortalized B cells.
Cherney BW; Bhatia K; Tosato G
Laboratory of Immunology, Food and Drug Administration, National Institutes of Health, Bethesda, MD 20892.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 20 **1994**, 91 (26) p12967-71, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
When deprived of autocrine growth factors, Epstein-Barr virus (EBV)-immortalized B cells stop growing and die. In this study, we show that death of EBV-immortalized cells deprived of autocrine growth factors occurred by apoptosis. Cycloheximide, a protein synthesis inhibitor, inhibited apoptosis, suggesting that de novo protein synthesis is required. Because p53, **Bcl-2**, and c-Myc were previously implicated in the induction or prevention of apoptosis in other systems, we assessed their possible involvement here. Unlike normal cells that respond to growth factor deprivation by down-regulating c-Myc expression, EBV-immortalized cells continued to express c-Myc, p53, and **Bcl-2** at levels comparable to those measured prior to starvation. Consistent with data demonstrating that c-Myc expression is sufficient to drive quiescent cells into the cell cycle, autocrine growth factor-deprived EBV-immortalized cells did not undergo growth arrest but rather continued to proliferate until death, which occurred randomly throughout the cell cycle. In contrast to EBV-immortalized B cells, normal peripheral blood B cells activated in vitro with anti-CD40 monoclonal antibody and interleukin 4 rapidly down-regulated c-Myc expression and underwent growth arrest in response to growth factors and serum deprivation. These findings demonstrated that c-Myc expression is deregulated in EBV-immortalized cells. Addition of **antisense** oligonucleotides to c-Myc specifically promoted the survival of starved EBV-immortalized cells and suppressed growth of nonstarved EBV-immortalized cells. Thus, deregulated expression of c-Myc in EBV-immortalized cells promotes proliferation and apoptosis following autocrine growth factor deprivation.

3/3,AB/127 (Item 127 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08188783 95045439
c-Myc induces cellular susceptibility to the cytotoxic action of TNF-alpha.
Klefstrom J; Vastrik I; Saksela E; Valle J; Eilers M; Alitalo K
Department of Pathology, University of Helsinki, Finland.
EMBO journal (ENGLAND) Nov 15 **1994**, 13 (22) p5442-50, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Tumor necrosis factor alpha (TNF) is a multifunctional cytokine which is cytotoxic for some tumor cells and transformed cells. The molecular mechanisms which render transformed and tumor cells sensitive to the cytotoxic action of TNF are unclear. We show here that an increased expression of the c-Myc oncoprotein strongly increases cellular sensitivity to TNF cytotoxicity. In Rat1A fibroblasts, which are resistant to TNF, the addition of TNF with a concomitant activation of a hormone-inducible c-Myc-estrogen receptor chimera (MycER) resulted in apoptotic cell death. Similarly, c-Myc overexpression enhanced the sensitivity of NIH3T3 fibroblasts to TNF-induced death. The c-Myc and TNF-induced apoptosis was inhibited by ectopic expression of the Bcl2 oncoprotein and by the free oxygen radical scavenging enzyme Mn superoxide dismutase. Furthermore, in highly TNF-sensitive fibrosarcoma cells, **antisense** c-myc oligodeoxynucleotides caused a specific inhibition of TNF cytotoxicity. Our results suggest that the deregulation of c-Myc, which is common in human tumors and tumor cell lines is one reason why these cells are TNF sensitive.

3/3,AB/128 (Item 128 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08187857 95021186
Tissue transglutaminase and apoptosis: sense and **antisense** transfection studies with human neuroblastoma cells.
Melino G; Annicchiarico-Petruzzelli M; Piredda L; Candi E; Gentile V; Davies PJ; Piacentini M
Department of Experimental Medicine, University of Rome Tor Vergata, Italy.
Molecular and cellular biology (UNITED STATES) Oct **1994**, 14 (10) p6584-96, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: CA-08748, CA, NCI; CA-41520, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this report, we show that the overexpression of tissue transglutaminase (tTG) in the human neuroblastoma cell line SK-N-BE(2) renders these neural crest-derived cells highly susceptible to death by apoptosis. Cells transfected with a full-length tTG cDNA, under the control of a constitutive promoter, show a drastic reduction in proliferative capacity paralleled by a large increase in cell death rate. The dying tTG-transfected cells exhibit both cytoplasmic and nuclear changes characteristic of cells undergoing apoptosis. The tTG-transfected cells express high **Bcl-2** protein levels as well as phenotypic neural cell adhesion molecule markers (NCAM and neurofilaments) of cells differentiating along the neuronal pathway. In keeping with these findings, transfection of neuroblastoma cells with an expression vector containing segments of the human tTG cDNA in **antisense** orientation resulted in a pronounced decrease of both spontaneous and retinoic acid (RA)-induced apoptosis. We also present evidence that (i) the apoptotic program of these neuroectodermal cells is strictly regulated by RA and (ii) cell death by apoptosis in the human neuroblastoma SK-N-BE(2) cells preferentially occurs in the substrate-adherent phenotype. For the first time, we report here a direct effect of tTG in the phenotypic maturation toward apoptosis. These results indicate that the tTG-dependent irreversible cross-linking of intracellular protein represents an important biochemical event in the induction of the structural changes featuring cells dying by apoptosis.

3/3,AB/129 (Item 129 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08186756 94366757
Antisense oligonucleotides suppress B-cell lymphoma growth in a

SCID-hu mouse model.
Cotter FE; Johnson P; [redacted]l P; Pocock C; al Mahdi N; Co[redacted] JK; Morgan G
LRF Department of Haematology and Oncology, Institute of Child Health, London.
Oncogene (ENGLAND) Oct **1994**, 9 (10) p3049-55, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The t(14;18) translocation is found in the majority follicular lymphomas and some high grade B-cell lymphomas. This is results in deregulation of the **BCL-2** gene and appears to play a role in oncogenesis. Various numbers of cells from a cell line derived spontaneously from a patient with B-cell lymphoma bearing the t(14;18) translocation and negative for the Epstein-Barr virus (EBV) were injected by IP, IV, and SC routes into SCID mice. The mice developed lymphoma bearing the t(14;18) translocation with as few as 5 x 10(6) cells within 28 days. This was determined by histological examination. The higher the cell inoculation the more rapidly the lymphoma developed. Engraftment of the tumour cells was determined by PCR for the t(14;18) breakpoint region on peripheral blood samples and could be detected prior to development of overt lymphoma. Having established a lymphoma model the cells were treated with **antisense** oligonucleotides to the first open reading frame of the **BCL-2** gene prior to inoculation of the SCID mice. Control treatments with sense and nonsense oligonucleotides was also performed. At 28 days the sense, nonsense and untreated cell SCID mice had developed lymphoma, however, the **antisense** treated group failed to develop lymphoma. The findings demonstrate the modelling of B-cell lymphoma bearing the t(14;18) translocation and the ability to modify the lymphoma process with the use of **antisense** oligonucleotides to the **BCL-2** gene. Reduction of the BCL2 protein suppresses the oncogenic potential of these lymphoma cells confirming that it plays an essential role in the development of malignancy.

3/3,AB/130 (Item 130 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08184324 94297233
Effects of **BCL-2 antisense** oligodeoxynucleotides on in vitro proliferation and survival of normal marrow progenitors and leukemic cells.
Campos L; Sabido O; Rouault JP; Guyotat D
Centre de Transfusion Sanguine, Lyon, France.
Blood (UNITED STATES) Jul 15 **1994**, 84 (2) p595-600, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous studies have shown that the **BCL-2** protooncogene encodes a mitochondrial protein that promotes cell survival by blocking programmed cell death. **Bcl-2** protein has been detected in normal immature myeloid cells and in acute myeloid leukemia (AML) cells. To assess its functional role in normal and leukemic hematopoiesis, we performed serum-free cultures of CD34+ normal marrow cells, of **bcl-2**-positive myeloid lines, and of AML cells in the presence of **bcl-2** sense, nonsense, and **antisense** phosphorothioate oligodeoxynucleotides. In all **antisense**-treated cultures, we observed (1) an inhibition of **bcl-2** protein expression by day 4 to 6 of culture; (2) a decrease in cell survival duration; and (3) a decrease in the number of clonogenic cells present in the culture. Moreover, exposure to chemotherapeutic drugs resulted in more effective killing of AML cells in the presence of **antisense** oligomers. We conclude that **bcl-2** protein is necessary for the survival of myeloid cells in culture, and that it may be implicated in the resistance of AML cells to chemotherapy.

3/3,AB/131 (Item 131 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08154792 95346689
Antisense oligonucleotide technology in the development of cancer therapeutics.
Tseng BY; Brown KD
Genta Inc., San Diego, CA 92130, USA.
Cancer gene therapy (UNITED STATES) Mar **1994**, 1 (1) p65-71, ISSN 0929-1903 Journal Code: CE3
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

3/3,AB/132 (Item 132 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08137445 95213071
Promotion and inhibition of activation-induced apoptosis in T-cell hybridomas by oncogenes and related signals.
Green DR; Mahboubi A; Nishioka W; Oja S; Echeverri F; Shi Y; Glynn J; Yang Y; Ashwell J; Bissonnette R
Division of Cellular Immunology, La Jolla Institute for Allergy and Immunology, CA 92037.
Immunological reviews (DENMARK) Dec **1994**, 142 p321-42, ISSN 0105-2896 Journal Code: GG4
Contract/Grant No.: GM52735, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
The Two Signal: Death/Survival Model suggests that cellular proliferation and physiological cell death should be intimately associated such that, in the absence of external influences, a normal cell departing from rest will have an equal probability of undergoing either process. The c-Myc protooncogene product has been implicated in cell cycle progression and in the control of gene expression, and more recently c-Myc has also been seen to promote apoptotic cell death. As predicted from the model, c-Myc-induced apoptosis is inhibited by growth factors or other anti-apoptotic signals including those provided by some oncogenes. Here, we discuss experiments that test the Two Signal: Death/Survival Model in the phenomenon of activation-induced apoptosis in T-cell hybridomas. Ligation of the antigen receptor on these cells leads to activation, resulting in cytokine production and apoptosis. Inhibition of c-Myc expression by addition of **antisense** oligodeoxynucleotides or transforming growth factor beta inhibits this form of apoptosis. Because c-Myc is known to bind to several cellular proteins, including Max, we further examined the effects of expression of a dominant negative Max on activation-induced apoptosis. We found that this Max mutant, which interferes with the function of the Myc/Max heterodimer, inhibits the induction of apoptosis by antigen receptor ligation. Thus, both Myc and Max play roles in activation-induced apoptosis, presumably via control of gene expression. Further, as predicted, signals generated from growth factor receptors or the v-Abl oncogene interfere with activation-induced apoptosis. In contrast, the anti-apoptotic effects of **Bcl-2** are not active in this form of apoptosis. Finally, a role for Fas/Fas-ligand interactions in activation-induced apoptosis is considered.

3/3,AB/133 (Item 133 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08039528 95037634
Reversal of chemoresis[redacted]ce of lymphoma cells by **antise**[redacted]-mediated reduction of **bcl-2** gene expression.
Kitada S; Takayama S; De Riel K; Tanaka S; Reed JC
La Jolla Cancer Research Foundation, Cancer Research Center, California 92037.
Antisense research and development (UNITED STATES) Summer **1994**, 4 (2) p71-9, ISSN 1050-5261 Journal Code: BI7
Contract/Grant No.: CA-60381, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The **bcl-2** gene is expressed in many types of human tumours and becomes transcriptionally deregulated in the majority of non-Hodgkin's lymphomas as the result of t(14;18) chromosomal translocations. The 26-kDa **Bcl-2** protein has been shown to block programmed cell death (apoptosis) induced by many types of stimuli, including a wide variety of chemotherapeutic drugs and radiation. The presence of **bcl-2** in tumor cells has been correlated with poor responses to therapy in patients with some types of cancer. To explore further the relevance of **bcl-2** to drug resistance, we used **antisense** (As) approaches to achieve reductions in the levels of steady state **Bcl-2** protein levels in t(14;18)-containing human lymphoma cell lines. Both synthetic **bcl-2** -As oligonucleotides and inducible expression plasmids that produce **bcl-2**-As transcripts induced reductions in **bcl-2** expression, resulting in a marked enhancement in the sensitivity of neoplastic cells to conventional chemotherapeutic drugs such as cytosine arabinoside (ara-C) and methotrexate (MTX). These results suggest that novel therapeutics targeted against **bcl-2** could provide the means for improved treatment of cancer by affecting physiological pathways distal to the targets of cytotoxic drugs.

3/3,AB/134 (Item 134 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08028652 95022631
Differential regulation of c-fos, fosB, c-jun, junB, **bcl-2** and bax expression in rat skin following single or chronic ultraviolet irradiation and in vivo modulation by **antisense** oligodeoxynucleotide superfusion.
Gillardon F; Eschenfelder C; Uhlmann E; Hartschuh W; Zimmermann M
II. Physiologisches Institut der Universitat, Heidelberg, Germany.
Oncogene (ENGLAND) Nov **1994**, 9 (11) p3219-25, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Single ultraviolet (u.v.) irradiation of mammalian cells in culture evokes the transcriptional activation of various proto-oncogenes, among them members of the fos/jun family which are known to play an important role in cell proliferation and differentiation. u.v. exposure of mammalian skin results in growth arrest and cell death followed by hyperproliferation of epidermal cells. To obtain information in vivo about a possible relationship between u.v.-induced proto-oncogene expression and cellular alterations, we have analysed the expression of c-fos, fosB, c-jun, junB, **bcl-2** and bax in rat epidermis after single and chronic u.v. irradiation. We present data demonstrating that the transcripts of these genes are constitutively expressed in the epidermis and that expression is differentially modulated by u.v. exposure. Single u.v. irradiation causes a rapid and sustained increase in c-jun, junB and c-fos mRNA and a decline in **bcl-2** transcripts, whereas expression of bax remained unchanged. c-Fos and c-Jun immunoreactivity was localized throughout the epidermal cell layers 1.5 h after single irradiation, but restricted to basal cells at 48 h suggesting an involvement in both u.v.-induced apoptosis and hyperproliferation. 48 h after chronic exposure a

significantly higher induction and a totally different pattern of epidermal proto-oncogene expression was detectable which may be associated with malignancy. Superfusion of rat skin with c-fos **antisense** oligodeoxynucleotides inhibited the increase in c-Fos immunolabeled epidermal cells 1.5 h after single u.v. irradiation demonstrating that **antisense** oligodeoxynucleotides are capable of penetrating mammalian skin and modulating the u.v. response in vivo. However, suppression of the early c-Fos activation did not significantly affect the formation of sunburn cells in the u.v.-exposed epidermis. Thus, c-Fos does not seem to play a major role in u.v.-induced apoptosis or other members of the fos/jun family may compensate for a loss in c-Fos.

3/3,AB/135 (Item 135 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07954597 94295993
Development of **antisense** therapeutics. Implications for cancer gene therapy.
Milligan JF; Jones RJ; Froehler BC; Matteucci MD
Gilead Sciences, Foster City, California 94404.
Annals of the New York Academy of Sciences (UNITED STATES) May 31 **1994**, 716 p228-41, ISSN 0077-8923 Journal Code: 5NM
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

3/3,AB/136 (Item 136 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07829795 94067789
Apoptosis in Burkitt lymphoma cells is driven by c-myc.
Milner AE; Grand RJ; Waters CM; Gregory CD
Department of Immunology, University of Birmingham Medical School, UK.
Oncogene (ENGLAND) Dec **1993**, 8 (12) p3385-91, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Chromosomal translocation and subsequent de-regulation of the c-myc proto-oncogene are considered to be critical events in the multi-stage evolution of Burkitt lymphoma (BL). It is widely accepted that Myc protein functions as a competence factor for proliferation. However, recent studies indicate that it can also act in some cell types as a regulator of apoptosis. BL cell populations display a high frequency of apoptosis in vivo, a property which is also readily demonstrable in vitro in group I BL cell lines. Such lines are known to retain the cell surface marker characteristics of the parental tumour cells and, in the case of Epstein-Barr virus-positive tumours, their restricted viral protein expression. We have shown previously that apoptosis in a group I BL cell line is inhibited by interferon (IFN)-alpha. Here we show that IFN-alpha-mediated suppression of apoptosis in group I BL cells corresponds temporally with inhibition of Myc protein levels. Furthermore, inhibition of Myc expression following treatment with c-myc anti-sense oligonucleotides markedly enhanced survival of group I BL cells. These results indicate that, whilst c-myc may facilitate cycling of tumour cells in which it is de-regulated, it also stimulates their apoptosis.

3/3,AB/137 (Item 137 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07825498 94003939

Investigations of **antisense** oligonucleotides targeted against **bcl-2** RNAs.
Kitada S; Miyashita T; Tanaka S; Reed JC
La Jolla Cancer Research Foundation, Cancer Research Center, California.
Antisense research and development (UNITED STATES) Summer **1993**, 3 (2) p157-69, ISSN 1050-5261 Journal Code: BI7
Contract/Grant No.: CA-60381, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Expression of the **bcl-2** gene becomes deregulated in many non-Hodgkin lymphomas as the result of t(14;18) chromosomal translocations. Because **bcl-2** regulates the survival of cells, and because its over-expression is associated with cellular resistance to killing by chemotherapeutic drugs and gamma-irradiation, this gene and its mRNA and protein products represent ideal targets for designing novel therapeutic strategies for the treatment of cancer. Here we describe the effects of an 18-mer phosphodiester oligonucleotide that is complementary to the first 6 codons of the **bcl-2** mRNA's open reading frame. When tested for inhibition of in vitro protein synthesis using RNAse-H-supplemented reticulocyte lysates and RNA prepared by in vitro transcription of a human **bcl-2** cDNA, the **bcl-2 antisense** (AS) oligomer completely abolished **Bcl-2** protein production at 10 microM, but had no effect on the in vitro translation of a chicken **bcl-2** RNA that contained three mismatches relative to the oligomer binding site on the human **bcl-2** RNA. A control 18-mer having the same base composition as the AS oligomer but with scrambled order (SC) was not inhibitory. Addition of AS and SC oligomers to cultures of a NIH-3T3 fibroblast cell line that had been stably infected with a recombinant retrovirus containing the same human **bcl-2** cDNA used for in vitro transcription/translation experiments revealed concentration-dependen t reductions in the relative levels of the 26-kD human **Bcl-2** protein (as determined by immunoblotting) by the AS but not by the SC oligomer. Similar results were obtained when AS and SC oligomers were applied to a t(14;18)-containing lymphoma cell line SU-DHL-4 that was cultured in low-serum media. When used at 200 microM, the **bcl-2** AS oligomer produced 84-95% reductions in **Bcl-2** protein levels in SU-DHL-4 cells but had relatively little effect on the levels of other mitochondrial control proteins, suggesting that the inhibitory effects were specific. Treatment of SU-DHL-4 cells with AS oligomer lead to essentially complete loss of **bcl-2** mRNA from cells within 1 day of addition to cultures, but presumably because of the long half-life of the **Bcl-2** protein (approximately 14 h), commensurate reductions in **Bcl-2** protein levels did not occur until 3 days.(ABSTRACT TRUNCATED AT 400 WORDS)

3/3,AB/138 (Item 138 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07802880 93373309
bcl-2 protein inhibits etoposide-induced apoptosis through its effects on events subsequent to topoisomerase II-induced DNA strand breaks and their repair [published erratum appears in Cancer Res 1994 Jun 1;54(11):3074]
Kamesaki S; Kamesaki H; Jorgensen TJ; Tanizawa A; Pommier Y; Cossman J
Department of Pathology, Georgetown University School of Medicine, Washington, D.C. 20007.
Cancer research (UNITED STATES) Sep 15 **1993**, 53 (18) p4251-6, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA-48716, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous studies have shown that **bcl-2** overexpression can inhibit apoptosis induced by DNA-damaging agents widely used in cancer

chemotherapy, including X-irradiation, alkylating agents (hydroperoxycyclophosphamide, etc.), and topoisomerase II inhibitors (etoposide, etc.). However, little is known about the mechanism by which **bcl-2** overexpression inhibits apoptosis triggered by these agents. In this study, we examined whether **bcl-2** overexpression could have effects on etoposide-induced DNA damage and its repair. For these experiments, we developed CH31 clones (mouse B-cells) stably transfected with human **bcl-2** sense plasmids and compared these clones with a parental CH31 clone or CH31 clones with **antisense** plasmids. Overexpression of **bcl-2** protein inhibited etoposide-induced apoptosis and cytotoxicity. However, there was no or little difference in the production and repair of DNA-protein cross-links, DNA single-strand breaks, and double-strand beaks among a parental CH31 clone and CH31 clones with human **bcl-2** sense or **antisense** plasmids. These findings indicate that (a) apoptosis or cytotoxicity induced by etoposide can be separated into early events (formation of double-strand breaks, DNA single-strand breaks, and double-strand breaks) and later events (secondary DNA fragmentation or cell death) and (b) **bcl-2** inhibits apoptosis and cytotoxicity induced by etoposide at some steps between these events.

3/3,AB/139 (Item 139 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07550990 93268758
Induction of apoptosis in blood cells from a patient with acute myelogenous leukemia by SC41661A, a selective inhibitor of 5-lipoxygenase.
Anderson KM; Levin J; Jajeh A; Seed T; Harris JE
Department of Medicine, Rush Medical College, Chicago, IL 60612.
Prostaglandins, leukotrienes, and essential fatty acids (SCOTLAND) Apr **1993**, 48 (4) p323-6, ISSN 0952-3278 Journal Code: P04
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Participation of leukotriene products in normal ex vivo hematopoiesis is well established. With increasingly specific inhibitors of lipoxygenases, it becomes possible to more closely define any participation of their biosynthetic products in these events. We cultured chronic myelogenous leukemia cells from the peripheral blood of several patients in blast crisis with three inhibitors of lipoxygenases: ETYA, and the more selective A63162 (Abbott) or SC41661A (Searle). All three agents reduced labelling of DNA with H3 thymidine measured at 4 h and reduced cell numbers by 72 h. An **antisense** deoxyoligonucleotide to the 5-lipoxygenase mRNA 'start' codon inhibited DNA synthesis at 24 h, as did two control oligonucleotides. Marked nuclear ultrastructural changes characteristic of apoptosis were induced by SC41661A in a subset of cells with the ultrastructure of promyelocytes. Whether this response characterizes a common pattern of this subset of leukemic cells to SC41661A, if damage to mitochondria with reduced function of **bcl-2** protooncogene product located at that site might have contributed or some other mechanism was responsible, and if inhibition of 5-lipoxygenase activity was involved, are questions to be decided in the future.

3/3,AB/140 (Item 140 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07466801 92199001
Antisense inhibition of oncogene expression.
Neckers L; Whitesell L; Rosolen A; Geselowitz DA
Clinical Pharmacology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
Critical reviews in oncogenesis (UNITED STATES) **1992**, 3 (1-2)

p175-231, ISSN 0893-9675 Journal Code: A1Y
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
To understand the role of individual genes in regulating biological processes, one must be able to interfere specifically with either their expression or function. While monoclonal antibodies have proven very useful in studying cell surface proteins, the specific inhibition of intracellular proteins in viable cells is a much more difficult problem. The goal of **antisense** technology is to develop small oligonucleotides, plasmids, or retroviral vectors which can be readily introduced into living cells in order to inhibit specific gene expression. In this review, we briefly describe the principles of **antisense** usage, including problems of cellular uptake and intracellular distribution, mechanism of **antisense** action, and the properties of various oligonucleotide derivatives. In addition we present several examples of the biological effects of **antisense** administration used to study the role of specific genes in the regulation of cell growth and differentiation.

3/3,AB/141 (Item 141 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07454961 91301181
Mitochondrial protein p26 BCL2 reduces growth factor requirements of NIH3T3 fibroblasts.
Reed JC; Talwar HS; Cuddy M; Baffy G; Williamson J; Rapp UR; Fisher GJ
University of Pennsylvania School of Medicine, Department of Pathology and Laboratory Medicine, Philadelphia 19104.
Experimental cell research (UNITED STATES) Aug **1991**, 195 (2) p277-83, ISSN 0014-4827 Journal Code: EPB
Contract/Grant No.: FO5DW04545; CA49576, CA, NCI; AR39691, AR, NIAMS; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The BCL2 (B cell lymphoma/leukemia-2) proto-oncogene encodes a 26-kDa protein that has been localized to the inner mitochondrial membrane and that has been shown to enhance the survival of some types of hematopoietic cells. Here we show that NIH3T3 fibroblasts stably transfected with a BCL2 expression plasmid exhibit reduced dependence on competence-inducing growth factors (platelet-derived growth factor, PDGF; epidermal growth factor, EGF) for initiation of DNA synthesis. The importance of BCL2 for growth factor-induced proliferation of these cells was further confirmed by the useage of BCL2 **antisense** oligodeoxynucleotides. The mechanisms by which overexpression of p26 BCL2 contributes to fibroblast proliferation are unknown, but do not involve alterations in: (a) the production of inositol triphosphates (IP3), (b) PDGF-induced transient elevations in cytosolic Ca2+ ions, or (c) the activity of protein kinase C enzymes in these transfected cells. The results imply that changes in mitochondrial functions play an important role in the early stages of the cell cycle that render 3T3 cells competent to respond to the serum progression factors that stimulate entry into S-phase.

3/3,AB/142 (Item 142 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07407460 94115767
Analysis of BCL2 and MYC expression in non-Hodgkin's lymphomas by in situ hybridization: correlation with chromosome translocations.
Murty VV; Ladanyi M; Houldsworth J; Mikraki V; Chaganti RS
Laboratory of Cancer Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
Diagnostic molecular pathology (UNITED STATES) Dec **1992**, 1 (4) p221-8, ISSN 1052-9551 Journal Code: BY3

Contract/Grant No.: CA [redacted]775, CA, NCI; CA-20194, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have used an in situ hybridization method for analysis of expression of BCL2 and MYC on cytospun preparations of normal and malignant lymphoid cell lines and tissue sections of normal and malignant lymph nodes. The probes comprised 50-mer **antisense** oligonucleotides starting at the ATG codons of exon 3 of BCL2 and exon 2 of MYC. We studied the expression of these two genes in frozen tissue sections of biopsy specimens derived from normal and hyperplastic lymph nodes, B-cell lymphomas carrying the t(14;18)(q32;q21) and t(8;14)(q24;q32) translocations, and T-cell lymphomas with clonal chromosome abnormalities. While all proliferating cells expressed both genes, BCL2 expression was increased two- to threefold in follicular lymphomas with t(14;18) and MYC expression was increased two- to four-fold in high-grade lymphomas with t(8;14). These results are consistent with previous data on deregulated expression of these genes obtained from study of lymphoma cell lines carrying the relevant translocations.

3/3,AB/143 (Item 143 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07303301 91004004

Antisense-mediated inhibition of BCL2 protooncogene expression and leukemic cell growth and survival: comparisons of phosphodiester and phosphorothioate oligodeoxynucleotides.

Reed JC; Stein C; Subasinghe C; Haldar S; Croce CM; Yum S; Cohen J
Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia 19104-6082.

Cancer research (UNITED STATES) Oct 15 **1990**, 50 (20) p6565-70, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA-47946, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Antisense oligodeoxynucleotides specific for sequences in mRNAs from the B-cell lymphoma/leukemia-2 (BCL2) gene were used to inhibit the growth in culture of a human leukemia cell line, 697. Normal phosphodiester (PO) and nuclease-resistant phosphorothioate (PS) oligodeoxynucleotides were compared with regard to specificity, potency, and kinetics. Both PO and PS **antisense** BCL2 oligodeoxynucleotides were specific inhibitors of cellular proliferation, since sense versions of these synthetic DNAs were inactive at similar concentrations. Specificity was further confirmed by quantitative immunofluorescence studies, showing that PO and PS **antisense** BCL2 oligodeoxynucleotides (when used at appropriate concentrations) reduced levels of BCL2 protein without influencing expression of HLA-DR and other control antigens. The onset of inhibition by PO oligodeoxynucleotides was faster, with reductions in cell numbers occurring within 1 day of addition to cultures, in contrast to phosphorothioates, which were ineffective until 3-4 days. Phosphorothioates were more potent that phosphodiesters, however, with half-maximal inhibition of leukemic cell growth occurring at concentrations 5-10 times lower. As expected from previous studies demonstrating the importance of BCL2 for regulating lymphoid cell survival, BCL2 **antisense** oligodeoxynucleotides also led to 697 leukemic cell death through sequence-specific mechanisms, with reductions in cellular viability generally lagging the inhibitory effects on cellular growth by about 2 days. Taken together, these data indicate that PO and PS oligodeoxynucleotides targeted against the human BCL2 protooncogene can be sequence-specific inhibitors of leukemic cell growth and survival.

3/3,AB/144 (Item 144 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07279581 93136502
Oligonucleotide therapy.
Crooke ST
Isis Pharmaceuticals, Carlsbad, California 92008.
Current opinion in biotechnology (ENGLAND) Dec **1992**, 3 (6) p656-61, ISSN 0958-1669 Journal Code: A92
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Rapid progress in oligonucleotide therapeutics has continued over the past year as major programs established in the past four years have grown and begun to be productive. Important advances were reported in the medicinal chemistry of oligonucleotides and in understanding their pharmacodynamic properties. Significant progress was made in understanding the pharmacokinetic and toxicologic properties of first generation analogs, particularly phosphorothioates and one oligonucleotide, ISIS 2105, entered clinical trials. Additionally, combinatorial approaches designed to identify oligonucleotides that may bind to a variety of targets were reported.

3/3,AB/145 (Item 145 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07231138 93310901
Selective anti-gene therapy for cancer: principles and prospects.
Cohen JS
Cancer Pharmacology Department, Georgetown University Medical School, Rockville, MD.
Tohoku journal of experimental medicine (JAPAN) Oct **1992**, 168 (2) p351-9, ISSN 0040-8727 Journal Code: VTF
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Oligodeoxynucleotides can act as **antisense** complements to target sense sequences of natural mRNAs to selectively regulate gene expression by translation arrest. This is a form of interventional gene therapy. Chemically modified analogs that are nuclease-resistant enable this strategy to be utilized in practice. Of the chemically modified backbone analogs of oligodeoxynucleotides we have used the phosphorothioate (PS) analog, in which a non-bridging phosphate oxygen atom is substituted with a sulfur atom. We have shown that these oligodeoxynucleotide analogs inhibit beta-globin expression in cell free systems, and that they are taken up by cells. Specific sequences have been shown to selectively regulate viral and cellular gene expression, for example the **bcl-2** oncogene that is found in ca. 90% of lymphomas. However, the PS analog has certain disadvantages, notably reduced hybridization and non-selective inhibition of translation. We have therefore synthesized a series of (PS-PO) co-polymers and characterized their properties. Other related approaches include catalytic **ribozymes** , and formation of triplexes by direct interaction of oligomers in the major groove of DNA. In general, a chemically modified oligodeoxynucleotide analog can be regarded as a novel form of informational drug.

3/3,AB/146 (Item 146 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05548262 21226802
Involvement of **bcl-2** and bax in photodynamic therapy-mediated apoptosis. **antisense bcl-2** oligonucleotide sensitizes rif 1 cells to photodynamic therapy apoptosis.
Srivastava M; Ahmad N; Gupta S; Mukhtar H

Department of Dermatology, Case Western Reserve University and Research Institute of University Hospitals of Cleveland, Cleveland, Ohio 44106.
Journal of biological chemistry (United States) **May 4 2001**, 276 (18) p15481-8, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article

Photodynamic therapy (PDT), a promising treatment modality, is an oxidative stress that induces apoptosis in many cancer cells in vitro and tumors in vivo. Understanding the mechanism(s) involved in PDT-mediated apoptosis may improve its therapeutic efficacy. Although studies suggest the involvement of multiple pathways, the triggering event(s) responsible for PDT-mediated apoptotic response is(are) not clear. To investigate the role of **Bcl-2** in PDT-mediated apoptosis, we employed **Bcl-2-antisense** and -overexpression approaches in two cell types differing in their responses toward PDT apoptosis. In the first approach, we treated radiation-induced fibrosarcoma (RIF 1) cells, which are resistant to silicon phthalocyanine (Pc 4)-PDT apoptosis, with **Bcl-2-antisense** oligonucleotide. This treatment resulted in sensitization of RIF 1 cells to PDT-mediated apoptosis as demonstrated by i) cleavage of poly(ADP-ribose) polymerase, ii) DNA ladder formation, iii) terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL)-positive cells, and iv) DEVDase activity. This treatment also resulted in oligonucleotide concentration-dependent decrease in cell viability and down-regulation of **Bcl-2** protein with a concomitant increase in apoptosis. However, the level of Bax, a pro-apoptotic member of **Bcl-2** family, remained unaltered. In the second approach, an overexpression of **Bcl-2** in PDT apoptosis-sensitive human epidermoid carcinoma (A431) cells resulted in enhanced apoptosis and up-regulation of Bax following PDT. In both the approaches, the increased Bax/**Bcl-2** ratio was associated with an increased apoptotic response of PDT. Our data also demonstrated that PDT results in modulation of other **Bcl-2** family members in a way that the overall ratio of pro-apoptotic and anti-apoptotic member proteins favors apoptosis.

3/3,AB/147 (Item 147 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05540183 21197838
Dominant-negative c-Jun promotes neuronal survival by reducing BIM expression and inhibiting mitochondrial cytochrome c release.
Whitfield J; Neame SJ; Paquet L; Bernard O; Ham J
Eisai London Research Laboratories, Bernard Katz Building, University College London, Gower Street, WC1E 6BT, London, United Kingdom.
Neuron (United States) Mar **2001**, 29 (3) p629-43, ISSN 0896-6273 Journal Code: AN8
Languages: ENGLISH
Document type: Journal Article

Sympathetic neurons require nerve growth factor for survival and die by apoptosis in its absence. Key steps in the death pathway include c-Jun activation, mitochondrial cytochrome c release, and caspase activation. Here, we show that neurons rescued from NGF withdrawal-induced apoptosis by expression of dominant-negative c-Jun do not release cytochrome c from their mitochondria. Furthermore, we find that the mRNA for BIM(EL), a proapoptotic **BCL-2** family member, increases in level after NGF withdrawal and that this is reduced by dominant-negative c-Jun. Finally, overexpression of BIM(EL) in neurons induces cytochrome c redistribution and apoptosis in the presence of NGF, and neurons injected with Bim **antisense** oligonucleotides or isolated from Bim(-/-) knockout mice die more slowly after NGF withdrawal.

3/3,AB/148 (Item 148 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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05537840 21159998
Activity of a novel **bcl-2**/bcl-xL-bispecific **antisense** oligonucleotide against tumors of diverse histologic origins.
Gautschi O; Tschopp S; Olie RA; Leech SH; Simoes-Wust AP; Ziegler A; Baumann B; Odermatt B; Hall J; Stahel RA; Zangemeister-Wittke U
Division of Oncology, Department of Internal Medicine, University Hospital, Zurich, Switzerland.
Journal of the National Cancer Institute (United States) **Mar 21 2001**, 93 (6) p463-71, ISSN 0027-8874 Journal Code: J9J
Languages: ENGLISH
Document type: Journal Article
BACKGROUND: Increased expression of the anti-apoptotic proteins **Bcl-2** and Bcl-xL is involved in the development and progression of many tumors. We recently reported that the **bcl-2**/bcl-xL-bispecific **antisense** oligonucleotide 4625 induces apoptosis in lung carcinoma cells. To further assess the therapeutic potential of oligonucleotide 4625, we investigated its effect on a series of human tumor cell lines of diverse histologic origins in vitro and in vivo. Methods: Oligonucleotide 4625-mediated inhibition of **bcl-2** and bcl-xL expression in vitro was measured in breast carcinoma cells with the use of reverse transcription-polymerase chain reaction (PCR), real-time PCR, and western blotting. Cytotoxicity was assessed in several different cell lines by measurement of tumor cell growth, propidium iodide uptake, and nuclear apoptosis. The in vivo activity of oligonucleotide 4625 was determined by the inhibition of growth of established tumor xenografts in nude mice, immunohistochemical staining of **Bcl-2** and Bcl-x proteins in the tumors, and western blotting of tumor lysates. Apoptosis in tumor xenografts was detected with the use of in situ TUNEL (i.e., terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-digoxigenin nick end labeling) staining. All statistical tests are two-sided. RESULTS: In breast carcinoma cells, oligonucleotide 4625 treatment reduced **bcl-2** and bcl-xL messenger RNA levels in a dose-dependent manner. At 600 nM:, oligonucleotide 4625 reduced **Bcl-2** and Bcl-xL protein levels to 25% (95% confidence interval [CI] = 16% to 34%) and 20% (95% CI = 14% to 26%), respectively, of the levels in untreated cells and it decreased viability in all cell lines mainly by inducing apoptosis. In vivo, oligonucleotide 4625 statistically significantly inhibited the growth of breast and colorectal carcinoma xenografts by 51% (95% CI = 28% to 74%) and 59% (95% CI = 44% to 74%), respectively, relative to those treated with control oligonucleotide 4626; it also reduced **Bcl-2** and Bcl-xL protein levels and induced tumor cell apoptosis. CONCLUSION: The **bcl-2**/bcl-xL-bispecific **antisense** oligonucleotide 4625 merits further study as a novel compound for cancer therapy.

3/3,AB/149 (Item 149 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

05536415 21161860
[Effect of WT1 gene expression on cell growth and proliferation in myeloid leukemia cell lines]
Mi Y; Wang L; Bian S
Institute of Hematology and Blood Diseases Hospital, CAMS and PUMC, Tianjin 300020.
Zhonghua xue ye xue za zhi (China) **Dec 1998**, 19 (12) p627-30, ISSN 0253-2727 Journal Code: CNL
Languages: CHINESE
Document type: Journal Article ; English Abstract
OBJECTIVE: To explore the effect of WT1 **antisense** oligonucleotide(AS-oligo) on cell proliferation and apoptosis in myeloid leukemia cell lines. METHODS: K562 and HL-60 cells were cultivated with WT1

AS-oligo. The cell proliferation, apoptosis, cell cycle and gene expression were examined by MTT colorimetry, FACS and RT-PCR. RESULTS: WT1 AS-oligo could inhibit the proliferation of K562 cell and induce apoptosis of K562 and HL-60 cells. On the contrary, the growth of HL-60 cells and the expression of WT1, mdm2 and **bcl-2** genes were unaffected. CONCLUSION: WT1 gene is related to the proliferation and apoptosis of leukemic cells. WT1 gene could suppress cell apoptosis independent of status of p53 and **bcl-2** genes. It might play an role in leukemogenesis.

3/3,AB/150 (Item 150 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05536398 21192318
bcl-2 Antisense treatment prevents induction of tolerance to focal ischemia in the rat brain.
Shimizu S; Nagayama T; Jin KL; Zhu L; Loeffert JE; Watkins SC; Graham SH; Simon RP
Department of Neurology, University of Pittsburgh, Pennsylvania 15213, USA.
Journal of cerebral blood flow and metabolism (United States) **Mar 2001**, 21 (3) p233-43, ISSN 0271-678X Journal Code: HNL
Contract/Grant No.: P01 NS35965, NS, NINDS; R01 NS24728, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
In the rat, 60 minutes of transient ischemia to the middle cerebral artery results in infarction of the caudate putamen. Ischemic preconditioning with 20 minutes of transient focal ischemia produced tolerance (attenuated infarction volume) to 60 minutes of subsequent focal ischemia administered three days, five days, or seven days later. Western blots from tolerant caudate putamen demonstrated increased **bcl-2** expression, maximum at 3 days and persisting through 7 days. Immunocytochemical examination found that **bcl-2** was expressed in cells with both neuronal and nonneuronal morphology in striatum after preconditioning ischemia. **bcl-2 antisense** oligodeoxynucleotides (ODNs), **bcl-2** sense ODNs, or artificial cerebrospinal fluid (CSF, vehicle) was infused into the lateral ventricle for the 72 hours between the 20-minute ischemic preconditioning and the 60-minute period of ischemia. **Antisense** ODN treatment reduced expression of **bcl-2** in the striatum and blocked the induction of tolerance by preconditioning ischemia. Sense and CSF treatments had no effect on either **bcl-2** expression or tolerance. In this model of induced tolerance to focal ischemia, **bcl-2** appears to be a major determinant.

3/3,AB/151 (Item 151 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05535542 21172806
Synergistic chemosensitization and inhibition of progression to androgen independence by **antisense Bcl-2** oligodeoxynucleotide and paclitaxel in the LNCaP prostate tumor model.
Leung S; Miyake H; Zellweger T; Tolcher A; Gleave ME
The Prostate Centre, Vancouver General Hospital, Vancouver, British Columbia, Canada.
International journal of cancer. Journal international du cancer (United States) Mar **15 2001**, 91 (6) p846-50, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Bcl-2 expression is up-regulated in prostate cancer cells

after androgen ablation and associated with development of androgen independence and chemoresistance. We recently reported that **antisense Bcl-2** oligodeoxynucleotides (ODNs) delay progression to androgen independence in the androgen-dependent (AD) human LNCaP prostate tumor model. The objectives in this study were to determine whether **antisense** human **Bcl-2** ODN enhances chemosensitivity of paclitaxel and whether combined **antisense Bcl-2** ODN and paclitaxel further delays time to androgen-independent (AI) progression in the LNCaP tumor model. Semi-quantitative reverse transcriptast-polymerase chain reaction revealed that treatment of LNCaP cells with **antisense Bcl-2** ODN decreased **Bcl-2** expression in a dose-dependent and sequence-specific manner, whereas **Bcl-2** expression was not affected by paclitaxel treatment. **Antisense Bcl-2** ODN treatment significantly enhanced paclitaxel chemosensitivity in vitro, reducing cell viability after treatment with 1 nM paclitaxel from 76% to 42%. Characteristic apoptotic DNA laddering was demonstrated after combined treatment with 500 nM **antisense Bcl-2** ODN and 1 nM paclitaxel but not with either agent alone. Adjuvant in vivo administration of combined **antisense Bcl-2** and polymeric micellar paclitaxel after castration resulted in a significant delay of emergence of AI recurrent LNCaP tumors compared with either agent alone. By 15 weeks post castration, tumor volume in mice treated with **antisense Bcl-2** ODN alone or mismatch control ODN plus paclitaxel was >3-fold higher than in mice treated with combined **antisense Bcl-2** ODN and paclitaxel. Mean serum prostate-specific antigen levels returned to or were above precastration levels by 11 weeks post castration in mice treated with **antisense Bcl-2** ODN alone or mismatch control ODN plus paclitaxel but remained 90% below the pre-castration level in mice treated with combined **antisense Bcl-2** ODN and paclitaxel. These findings identify combined **antisense Bcl-2** and paclitaxel as a potentially new therapeutic strategy for advanced prostate cancer by enhancing paclitaxel chemosensitivity and delaying progression of hormone-refractory prostate cancer. Copyright 2001 Wiley-Liss, Inc.

3/3,AB/152 (Item 152 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05533459 21110358

Bcl-2 down-regulation causes autophagy in a caspase-independent manner in human leukemic HL60 cells.

Saeki K; Yuo A; Okuma E; Yazaki Y; Susin SA; Kroemer G; Takaku F
Department of Hematology, Research Institute, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.

Cell death and differentiation (England) Dec 2000, 7 (12) p1263-9, ISSN 1350-9047 Journal Code: C7U
Languages: ENGLISH
Document type: Journal Article

To understand the roles of **bcl-2** for the survival of leukemic cells, we constructed human leukemic HL60 transformant lines in which full length **bcl-2 antisense** message was conditionally expressed by a tetracycline-regulatable expression system. Cell growth was completely inhibited after **antisense** message induction and massive cell death was induced. Electron microscopic examinations show that cells died by autophagy, but not by apoptosis. The morphology and the function of mitochondria remained intact: neither the reduction in mitochondrial membrane potential nor the nuclear translocation of AIF, a mitochondrial protein that translocates to nuclei in cases of apoptosis, was observed. Caspase inhibitors did not rescue **bcl-2-antisense**-mediated autophagy. Thus, **bcl-2** is essential for leukemic cell survival and its down-regulation results in autophagy. Cell Death and Differentiation (2000) 7, 1263 - 1269.

3/3,AB/153 (Item 1[redacted]rom file: 155)
DIALOG(R)File 155:MEDLINE(R)

05533014 21115158
The decrease of PKCalpha is associated with hepatic apoptosis at early and late phases of polymicrobial sepsis.
Jao HC; Yang RC; Hsu HK; Hsu C
Department of Physiology, Kaohsiung Medical College, Taiwan.
Shock (United States) Feb 2001, 15 (2) p130-4, ISSN 1073-2322
Journal Code: CAE
Languages: ENGLISH
Document type: Evaluation Studies; Journal Article
The present study investigates the relationship between the PKC-alpha and hepatic apoptosis during sepsis. Cecal ligation and puncture- (CLP) induced animal model of polymicrobial sepsis was used, with early and late sepsis referring to those animals sacrificed at 9 and 18 h, respectively, after CLP. The expressions of PKCalpha and **Bcl-2** family proteins as well as poly(ADP-ribose) polymerase (PARP) cleavage were quantified to evaluate the possible factors involved in the hepatic cell death during sepsis. The apoptosis of hepatocytes under septic condition or hepatocytes treated with PKCalpha **antisense** was evaluated by gel electrophoresis and/or flow cytometry after Annexin-V-Fluos and propidium iodide staining. The results indicated that (1) the protein expression of membrane-associated PKCalpha was decreased at early ($P < 0.05$) and late ($P < 0.01$) sepsis; (2) the protein expressions of **Bcl-2** and Bcl-xL were decreased, whereas Bax expression was increased at late sepsis; (3) the percentage of PARP cleavage was increased at early ($P < 0.05$) and late ($P < 0.01$) sepsis; (4) severe DNA fragmentation was observed at late sepsis; (5) the apoptotic cell population was increased at early and late sepsis; and (6) the percentage of apoptotic cell population in PKCalpha **antisense** -treated cells was significantly higher than that in untreated cells. These results suggest that inactivation of PKCalpha may play an important role in modulating hepatic apoptosis during sepsis and the apoptosis is closely associated with the alterations of **Bcl-2** family proteins.

3/3,AB/154 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12229524 BIOSIS NO.: 199900524373
Hammerhead **ribozyme**-mediated disruption of **Bcl-2** induces apoptosis and blocks cell cycle progression through the proteolytic degradation of cyclin A in vascular smooth muscle cells.
AUTHOR: Perlman Harris R(a); Krasinski Kevin; Sata Masataka; Dorai Thambi; Buttyan Ralph; Walsh Kenneth
AUTHOR ADDRESS: (a)Tufts Univ., Boston, MA**USA
JOURNAL: Circulation 98 (17 SUPPL.):pI597-I598 Oct. 27, **1998**
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/155 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11919060 BIOSIS NO.: 199900165169

Bcl-2 antisense expression sensitizes U118 MG cells to cisplatin-induced cell death.
AUTHOR: Zhu C J; Wu M; Tan Y; Li Y B; Tung M; Wong M C
AUTHOR ADDRESS: Dep. Neurol., Singapore Gen. Hosp.**Singapore
JOURNAL: Cancer Gene Therapy 5 (6 CONF. SUPPL.):pS22 Nov.-Dec., **1998**
CONFERENCE/MEETING: Seventh International Conference on Gene Therapy of Cancer San Diego, California, USA November 19-21, 1998
ISSN: 0929-1903
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/156 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11865422 BIOSIS NO.: 199900111531
The effect of **Bcl-2 antisense** oligonucleotides in B-CLL in vitro survival.
AUTHOR: Pepper C(a); Hoy T; Bentley B
AUTHOR ADDRESS: (a)Dep. Haematology, Llandough Hospital, Penarth, South Glamorgan CF64 2XX**UK
JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p187B Nov. 15, **1998**
CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/157 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11862859 BIOSIS NO.: 199900108968
Inhibition of **Bcl-2** with liposomal P-ethoxy **antisense** oligonucleotides induces apoptosis in the presence of high level of Bcl-XL and is critically depending on baseline **Bcl-2** levels in AML.
AUTHOR: Konopleva M; Tari A; Estrov Z; Harris D; Lopez-Beresein G; Andreeff M
AUTHOR ADDRESS: U Texas MD Anderson Cancer Cent., Houston, TX**USA
JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p510A-511A Nov. 15, **1998**
CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/158 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11852612 BIOSIS NO.: 199900098721
Correlation of the expression of a naturally occuring **bcl-2 antisense** RNA and the **BCL-2** protein in hematopoetic but not in breast cancer cell lines.
AUTHOR: Bertram J; Hiddemann W; Kneba M
AUTHOR ADDRESS: Dep. Hematol./Oncol., Univ. Clin., R. Koch Str. 40,

Goettingen**Germany
JOURNAL: Annals of Hematology 77 (SUPPL. 2):pS218 **1998**
CONFERENCE/MEETING: Annual Congress of the German and Austrian Societies of Hematology and Oncology Frankfurt, Germany October 25-28, 1998
SPONSOR: Austrian Society of Hematology and Oncology
ISSN: 0939-5555
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/159 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11799674 BIOSIS NO.: 199900045783
BCL-2 antisense treatment blocks induced tolerance to focal cerebral ischemia in the rat.
AUTHOR: Simon R P; Shigetoshi S; Zhu R; Graham S H; Henshall D C; Goss J R
AUTHOR ADDRESS: Dep. Neurol., Univ. Pittsburgh, Biomedical Science Tower S5, Pittsburgh, PA 15213**USA
JOURNAL: Society for Neuroscience Abstracts 24 (1-2):p253 **1998**
CONFERENCE/MEETING: 28th Annual Meeting of the Society for Neuroscience, Part 1 Los Angeles, California, USA November 7-12, 1998
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/160 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11739034 BIOSIS NO.: 199800519730
Antisense comes of age.
AUTHOR: Flanagan W Michael(a)
AUTHOR ADDRESS: (a)333 Lakeside Drive, Foster City, CA 94404**USA
JOURNAL: Cancer and Metastasis Reviews 17 (2):p169-176 June, **1998**
ISSN: 0167-7659
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/161 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11675986 BIOSIS NO.: 199800457717
Formation and delivery of novel oligonucleotide/cationic lipid complexes.
AUTHOR: Wong France M P(a); Macadam Sheina A(a); Kim Anne(a); Zhang Yuan-Peng; Klasa Richard(a); Brown Bob D; Bally Marcel B(a)
AUTHOR ADDRESS: (a)Dep. Advanced Therapeutics, B.C. Cancer Agency, 600 West 10th Ave., Vancouver, BC V5Z 4E6**Canada
JOURNAL: Journal of Liposome Research 8 (1):p126 Feb., **1998**
CONFERENCE/MEETING: Sixth Liposome Research Days Conference Les Embiez, France May 28-31, 1998
ISSN: 0898-2104
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/162 (Item 9 [redacted]m file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11675875 BIOSIS NO.: 199800457606
Signal transduction as a target for novel cancer therapeutics.
AUTHOR: Lopez-Berestein Gabriel(a)
AUTHOR ADDRESS: (a)Dep. Biommunotherapy, Sect. Immunobiol. and Drug Carriers, Univ. Texas, MD Anderson Cancer Cente**USA
JOURNAL: Journal of Liposome Research 8 (1):p20-21 Feb., **1998**
CONFERENCE/MEETING: Sixth Liposome Research Days Conference Les Embiez, France May 28-31, 1998
ISSN: 0898-2104
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/163 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11557010 BIOSIS NO.: 199800338342
In vivo modelling of gene silencing therapy in haematological malignancies: Apoptosis sensitisation approaches.
AUTHOR: Fennell D A; Corbo M; Kuss B; Cotter F E
AUTHOR ADDRESS: LRF Molecular Haematology Unit, Inst. Child Health, 30 Guilford St., London WC1N 1EH**UK
JOURNAL: British Journal of Haematology 101 (SUPPL. 1):p103 May, **1998**
CONFERENCE/MEETING: Annual Scientific Meeting of the British Society for Haematology Glasgow, Scotland, UK April 27-30, 1998
SPONSOR: British Society for Haematology
ISSN: 0007-1048
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/164 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11541996 BIOSIS NO.: 199800323328
Pharmacokinetics, tissue distribution, and safety of P-ethoxy oligonucleotides incorporated in liposomes.
AUTHOR: Tari Ana M; Stephens Clifton; Rosenblum Michael; Lopez-Berestein Gabriel(a)
AUTHOR ADDRESS: (a)Dep. Bioimmunotherapy, Univ. Texas M.D. Anderson Cancer Cent., Houston, TX**USA
JOURNAL: Journal of Liposome Research 8 (2):p251-264 May, **1998**
ISSN: 0898-2104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: P-ethoxy oligonucleotides (oligos) are lipophilic analogs of phosphodiesters. We have used liposomes to increase the intracellular uptake of P-ethoxy oligos, and demonstrated that liposomal P-ethoxy **antisense** oligos specific for Bcr-Abl, Grb2, Crk1 or **Bcl-2** mRNA could selectively inhibit the production of the corresponding proteins, thereby inducing growth inhibition in leukemia and lymphoma cell lines. In support of studying the effectiveness of liposomal P-ethoxy **antisense** oligos in animal models, we had

conducted a series of studies to evaluate the pharmacokinetics, tissue distribution and safety of intravenous injection of liposomal P-ethoxy oligos in normal mice. The pharmacokinetics and tissue distribution of liposomal P-ethoxy oligos are very similar to those of other liposomal compounds. The plasma clearance rate of liposomal P-ethoxy oligos was biphasic; the t1/2alpha and t1/2beta were approximately 6.7 min and 7 h, respectively. The highest concentrations of liposomal P-ethoxy oligos were found in spleen and liver, with a t1/2 of approximately 48 h. When up to 180 mg of P-ethoxy oligos per kg of mice's body weight were used, the administration of liposomal P-ethoxy oligos had no adverse effects on renal and hepatic functions, or on the hematological parameters studied. No major organ pathologic changes were observed. Our studies suggested that, at the doses studied, liposomal P-ethoxy oligos could be safely used in animal studies. Since liposomal P-ethoxy oligos were found to accumulate mainly in spleen and liver, which are the major organs of leukemic and lymphoma disease manifestation, we are currently investigating the use of liposomal P-ethoxy **antisense** oligos in experimental leukemia and lymphoma animal models.

1998

3/3,AB/165 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11511436 BIOSIS NO.: 199800292768
bcl-2 Antisense oligonucleotides inhibit Merkel cell carcinoma growth in SCID mice.
AUTHOR: Schlagbauer-Wadl H(a); Moll I; Waltering S; Eichler H-G; Wolff K(a); Pehamberger H(a); Jansen B(a)
AUTHOR ADDRESS: (a)Dep. Dermatol., Div. Gen. Dermatol., Vienna**Austria
JOURNAL: Journal of Dermatological Science 16 (SUPPL. 1):pS135 March, **1998**
CONFERENCE/MEETING: Third Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology, Society for Investigative Dermatology Cologne, Germany May 7-10, 1998
SPONSOR: European Society for Dermatological Research
ISSN: 0923-1811
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/166 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11426775 BIOSIS NO.: 199800208107
Bcl-2-independent Bcr-Abl-mediated resistance to apoptosis: Protection is correlated with up regulation of Bcl-x|L.
AUTHOR: Amarante-Mendes Gustavo P(a); McGahon Anne J; Nishioka Walter K; Afar Daniel E H; Witte Owen N; Green Douglas R
AUTHOR ADDRESS: (a)Dep. Imunol., Inst. Cienc. Biomed., Univ. Sao Paulo, Sao Paulo 05508-900**Brazil
JOURNAL: Oncogene 16 (11):p1383-1390 March 19, **1998**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bcr-Abl is the molecule responsible for both the transformation phenotype and the resistance to chemotherapeutic drugs found in chronic myelogenous leukemia (CML) cells. Wild-type HL-60, a transformed pro-myelocytic cell line, is very susceptible to apoptosis-inducing

agents. We show here that expression of Bcr-Abl in HL-60 cells rendered them extremely resistant to apoptosis induced by a wide variety of agents. The anti-apoptotic effect of Bcr-Abl was found to be independent of the phase of the cell cycle. Treatment with **antisense** oligonucleotides directed to bcr decreased the expression of the ectopic bcr-abl and restored susceptibility to apoptosis. Double mutations affecting the autophosphorylation site and the phosphotyrosine-binding motif (FLVRES) have been previously shown to impair the transforming activity of Bcr-Abl in fibroblasts and hematopoietic cells, however HL-60 cells expressing this double mutant molecule exhibited the same level of resistance to apoptosis as those expressing the wild-type Bcr-Abl. Interestingly, wild type and mutant Bcr-Abl induced in HL-60 cells a dramatic down regulation of **Bcl-2** and increased the levels of Bcl-x|L. The level of Bax did not change in response to the presence of Bcr-Abl. **Antisense** oligonucleotides targeted to bcl-x down-regulated the expression of Bcl-x, and increased the susceptibility of HL-60.Bcr-Abl cells to staurosporine. Importantly, HL-60 cells overexpressing Bcl-x|L showed higher expression of Bcl-X|L but lower resistance to apoptosis when compared to HL-60.Bcr-Abl cells. The results described here show that Bcr-Abl is a powerful mammalian anti-apoptotic molecule and can act independently of **Bcl-2**. Bcl-X|L, however, seems to participate in part in Bcr-Abl-mediated resistance to apoptosis in HL-60 cells.

1998

3/3,AB/167 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11416420 BIOSIS NO.: 199800197752
Evidence for a naturally occurring **bcl-2 antisense** transcript which is not restricted to the t(14/18) translocation.
AUTHOR: Bertram J; Krieger G; Hiddemann W; Kneba M
AUTHOR ADDRESS: Dep. Hematol./Oncol., Univ. Clinics, R. Koch Str. 40, Goettingen**Germany
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p571 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/168 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11416081 BIOSIS NO.: 199800197413
Clinical pharmacokinetics of G3139, oligonucleotide **antisense** to **bcl-2**.
AUTHOR: Raynaud F(a); Foster L(a); Judson I(a); Clarke P A(a); Waters J; Cunningham D; Cotter F
AUTHOR ADDRESS: (a)CRC Cent. Cancer Therapeutics, Inst. Cancer Res., London **UK
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p521 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X

RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/169 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11415378 BIOSIS NO.: 199800196710
Bcl-2 antisense oligodeoxynucleotide 2009 synergizes with chemotherapy on lung cancer cell lines and has antitumor activity against lung cancer xenografts.
AUTHOR: Zangemeister-Wittke U(a); Fabbro D; Mueller M; Schenker T; Stahel R A
AUTHOR ADDRESS: (a)Div. Oncol., Dep. Intern. Med., Univ. Hosp. Zurich, CH-8044 Zurich**Switzerland
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p417 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/170 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11415377 BIOSIS NO.: 199800196709
Antisense oligodeoxynucleotides designed to downregulates the expression of bcl-x|L and of **bcl-2** and bcl-x|L simultaneously, restore the apoptotic response of lung cancer cell lines.
AUTHOR: Leudke G H; Leech S H; Stahel R A; Zangemeister-Wittke U
AUTHOR ADDRESS: Div. Oncol., Dep. Intern. Med., University Hosp. Zurich, CH-8044 Zurich**Switzerland
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p417 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/171 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11414401 BIOSIS NO.: 199800195733
Antisense to the EBV-encoded latent membrane protein 1 (LMP-1) suppresses LMP-1 and **Bcl-2** expression and promotes apoptosis in EBV-immortalized B-cells.
AUTHOR: Kenney J L(a); Guinness M E; Curiel T; Lacy J
AUTHOR ADDRESS: (a)Yale Univ. Sch. Med., New Haven, CT 06520**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p272 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research

ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

3/3,AB/172 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11406923 BIOSIS NO.: 199800188255
Correction of PREVIEWS 99525814. Establishing apoptosis resistant cell lines for improving protein productivity of cell culture. Addition of author name. Erratum published in Cytotechnology Vol. 26. Iss. 1. 1998. p. 79.
AUTHOR: Suzuki Eiji(a); Terada Satoshi; Ueda Hiroshi; Fujita Tetsuo; Komatsu Tomoaki; Kim Yon Hui; Takayama Shinichi; Reed John C
AUTHOR ADDRESS: (a)Dep. Chem. Biotechnol., Graduate Sch. Engineering, Univ. Tokyo, Hongo, Bunkyoku, Tokyo 113**Japan
JOURNAL: Cytotechnology 26 (1):p55-59 **1998**
ISSN: 0920-9069
DOCUMENT TYPE: Article; Article; Erratum
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The authors established apoptosis resistant COS-1, myeloma, hybridoma, and Friend leukemia cell lines by genetically engineering cells, aiming at more efficient protein production by cell culture. COS-1 cells, which are most widely used for eukaryotic gene expression, were transfected with human **bcl-2** gene. Both **bcl-2** and mock transfected COS-1 cells were cultured at low (0.2%) serum concentration for 9 days. The final viable cell number of the **bcl-2** transfected cells was nine-fold of that of the mock transfectants. Both **bcl-2** and mock transfectants were further transfected with the vector pcDNA-lambda containing SV40 ori and immunoglobulin lambda gene for transiently expressing lambda protein. The **bcl-2** expressing COS-1 cells produced more lambda protein than the mock transfected COS-1 cells after 4 days posttransfection. Mouse myeloma p3-X63-Ag.8.653 cells, which are widely used as the partner for preparing hybridoma, and hybridoma 2E3 cells were transfected with human **bcl-2** gene. Both **bcl-2** transfected myeloma and hybridoma survived longer than the corresponding original cells in batch culture. The **bcl-2** transfected 2E3 cells survived 2 to 4 four days longer in culture, producing 1.5- to 4-fold amount of antibody in comparison with the mock transfectants. Coexpression of bcl-1 with **bcl-2** improved survival of hybridoma 2E3 cells more than **bcl-2** expression alone. The bcl-1 and **bcl-2** coexpressing cells produced more IgG than the cells expressing **bcl-2** alone. Apoptosis of Friend murine erythroleukemia (F-MEL) cells was suppressed with **antisense** c-jun expression. The **antisense** c-jun expressing cells survived 16 days at non-growth state.

1998

3/3,AB/173 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11328208 BIOSIS NO.: 199800109540
Antisense oligonucleotide of the MCL-L gene, A **BCL-2** related gene, blocks granulocytic and macrophagic differentiation.
AUTHOR: Calabresse C(a); Chomienne C; Evan G(a)
AUTHOR ADDRESS: (a)Biochem. Cell Nucleus Lab., Imperial Cancer Res. Fund, London**UK

JOURNAL: Anticancer Research 17 (5C):p3954-3955 Sept.-Oct., **1997**
CONFERENCE/MEETING: Seventh International Conference on Differentiation Therapy Versailles, France October 5-8, 1997
ISSN: 0250-7005
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/174 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11325649 BIOSIS NO.: 199800106981
Antisense Bcl-2 oligodeoxynucleotide uptake in tumour cell lines.
AUTHOR: Cunningham A J(a); Alexandroff A B
AUTHOR ADDRESS: (a)John Hughes Bennett Lab., Dep. Haematol., Western General Hosp., Edinburgh EH4**UK
JOURNAL: Immunology 92 (SUPPL. 1):p14 Dec., **1997**
CONFERENCE/MEETING: 5th Annual Congress of the British Society for Immunology Brighton, England, UK December 2-5, 1997
SPONSOR: British Society for Immunology
ISSN: 0019-2805
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/175 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11287266 BIOSIS NO.: 199800068598
Activity of **BCL-2 antisense** molecular G3139 against, lymphoma/leukemia: Results from a phase I/IIA clinical trial and further developments.
AUTHOR: Cotter F(a); Webb A; Cunningham D; Fennell D; Corbo M; Ross P; Walters J; Judson I; Raynaud F; Clarke P; Dziewanowska Z E
AUTHOR ADDRESS: (a)Inst. Child Health, Royal Marsden Hosp., Marsden**UK
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p514A Nov. 15, **1997**
CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/176 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11287177 BIOSIS NO.: 199800068509
Inhibition of **Bcl-2** with liposomal-delivered **antisense** oligonucleotides (AS-ODN) induces apoptosis and increases the sensitivity of primary acute myeloid leukemia (AML) cells and cell lines to cytosine arabinoside and doxorubicin.
AUTHOR: Konopleva M; Tari A; Lopez-Berestein G; Andreeff M
AUTHOR ADDRESS: Univ. Texas M.D. Anderson Cancer Cent., Houston, TX**USA
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p494A Nov. 15, **1997**
CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/177 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11211544 BIOSIS NO.: 199799832689
A **Bcl-2 antisense** oligodeoxynucleotide increases AMPA toxicity in cortical cultures.
AUTHOR: Irvin S M(a); Sinor A D; White M J; Chen J; Zhu R L; Dicaprio M J; Jia K; Greenberg D A
AUTHOR ADDRESS: (a)Dep. Neurol., Univ. Pittsburgh Sch. Med., Pittsburgh, PA 15261**USA
JOURNAL: Society for Neuroscience Abstracts 23 (1-2):p2178 **1997**
CONFERENCE/MEETING: 27th Annual Meeting of the Society for Neuroscience New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/178 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11164090 BIOSIS NO.: 199799785235
Protein kinase C-beta-II activation by 1-beta-D-arabinofuranosylcytosine is antagonistic to stimulation of apoptosis and **Bcl-2**-alpha down-regulation.
AUTHOR: Whitman Susan P; Civoli Francesca; Daniel Larry W(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Bowman Gray Sch. Med., Wake Forest Univ., Medical Center Blvd., Winston-Salem, NC**USA
JOURNAL: Journal of Biological Chemistry 272 (38):p23481-23484 **1997**
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1-beta-D-Arabinofuranosylcytosine (ara-C) stimulates the formation of both diglyceride and ceramide in the acute myelogenous leukemia cell line HL-60 (Strum, J. C., Small, G. W., Pauig, S. B., and Daniel, L. W. (1994) J. Biol. Chem 269, 15493-15497). ara-C also causes apoptosis in HL-60 cells which can be mimicked by exogenous ceramide. However, the signaling role for ara-C-induced diacylglycerol (DAG) is not defined. We found that **Bcl-2** levels were increased by treatment of HL-60 cells with exogenous DAG or 12-O-tetradecanoylphorbol-13-acetate (TPA). In contrast, exogenous ceramide treatment caused a decrease in cellular **Bcl-2** levels. Thus, ara-C stimulates the synthesis of two second messengers with opposing effects on **Bcl-2**. Since the effects of ara-C-induced DAG could be due to protein kinase C (PKC) activation, we determined the effects of ara-C on PKC isozymes. ara-C caused an increase in membrane-bound PKC-beta-II (but not PKC-alpha or PKC-delta). ara-C or TPA-induced translocation of PKC-beta-II was inhibited by 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine (ET-18-OCH-3), and ara-C-induced apoptosis was stimulated by pretreatment of the cells with ET-18-OCH-3. ET-18-OCH-3 also inhibited stimulation of **Bcl-2** by TPA and enhanced the decrease in **Bcl-2** observed in ara-C-treated cells. These data indicate that ara-C-induced apoptosis is limited by ara-C-stimulated PKC-beta-II through effects on **Bcl-2**. To further determine the role of PKC, we used **antisense**

oligonucleotides directed toward PKC-beta-II. The **antisense**, but not the sense, oligonucleotide inhibited PKC-beta-II activation and enhanced ara-C-induced apoptosis. These data demonstrate that the stimulation of apoptosis by ara-C is self-limiting and can be enhanced by inhibition of PKC.

1997

3/3,AB/179 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11058313 BIOSIS NO.: 199799679458
First demonstration of anti-lymphoma activity of **BCL-2** **antisense** molecule-G3139: Results of phase I/IIA clinical trial.
AUTHOR: Webb A(a); Cunningham D(a); Cotter F; Ross P(a); Walters J; Judson I(a); Raynaud F(a); Clarke P(a); Dziewanowska Z E
AUTHOR ADDRESS: (a)Royal Marsden Hosp., Sutton, Surrey**UK
JOURNAL: British Journal of Cancer 76 (SUPPL. 1):p33 **1997**
CONFERENCE/MEETING: Joint Meeting of the British Oncological Association, Association of Cancer Physicians and the Royal College of Radiologists St. Andrews, Scotland, UK July 5-8, 1997
ISSN: 0007-0920
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/180 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11054822 BIOSIS NO.: 199799675967
Downregulation of **bcl-2** by **antisense** oligonucleotides reduces tumor size and improves chemosensitivity of human melanoma in SCID mice.
AUTHOR: Jansen B(a); Wadl H(a); Brown D B; Bryan R; Wolff K(a); Eichler H-G ; Pehamberger H(a)
AUTHOR ADDRESS: (a)Dep. Dermatol./Div. General Dermatol., Waehringer Guertel 18-20, 1090 Vienna**Austria
JOURNAL: Melanoma Research 7 (SUPPL. 1):pS139 **1997**
CONFERENCE/MEETING: 4th World Conference on Melanoma Sydney, Australia June 10-14, 1997
ISSN: 0960-8931
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/181 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11006252 BIOSIS NO.: 199799627397
Potential of **antisense** oligomers to **bcl-2** for purging of minimal residual disease in bone marrow and peripheral blood stem cell harvests in acute myeloid leukaemia.
AUTHOR: Cunningham A J; Rogers S Y; Craig J I O; Antohny R S; Parker A C
AUTHOR ADDRESS: Leukaemia Res. Lab., Dep. Haematol., Edinburgh Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW**UK
JOURNAL: British Journal of Haematology 97 (SUPPL. 1):p58 **1997**
CONFERENCE/MEETING: Annual Scientific Meeting of the British Society for Haematology Harrogate, England, UK April 14-17, 1997
ISSN: 0007-1048

RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/182 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10909400 BIOSIS NO.: 199799530545
Antisense oligonucleotides targeting sequences shared by the **Bcl-2** and Bcl-xL mRNA efficiently downregulate expression of both proteins and induce apoptosis of lung cancer cells.
AUTHOR: Luedke G H; Ziegler A; Stahel R A; Zangemeister-Wittke U
AUTHOR ADDRESS: Div. Oncol., Dep. Internal Med., Univ. Hosp., CH-8091 Zurich**Switzerland
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 38 (0):p170 **1997**
CONFERENCE/MEETING: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/183 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10909162 BIOSIS NO.: 199799530307
An **antisense bcl-2** oligonucleotide alters cell proliferation, viability and programmed cell death in non-small cell lung cancer cell lines.
AUTHOR: Koty P P; Mayotte J; Levitt M L
AUTHOR ADDRESS: Allegheny Univ. Health Sci., Pittsburgh, PA 15212**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 38 (0):p135 **1997**
CONFERENCE/MEETING: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/184 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10904669 BIOSIS NO.: 199799525814
Establishing apoptosis resistant cell lines for improving protein productivity of cell culture.
AUTHOR: Suzuki Eiji(a); Terada Satoshi; Ueda Hiroshi; Fujita Tetsuo; Komatsu Tomoaki; Takayama Shinichi; Reed John C
AUTHOR ADDRESS: (a)Dep. Chem. Biotechnol., Graduate Sch. Engineering, Univ. Tokyo, Hongo, Bunkyoku, Tokyo 113**Japan
JOURNAL: Cytotechnology 23 (1-3):p55-59 **1997**
ISSN: 0920-9069
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The authors established apoptosis resistant COS-1, myeloma,

hybridoma, and Friend leukemia cell lines by genetically engineering cells, aiming at more efficient protein production by cell culture. COS-1 cells, which are most widely used for eukariotic gene expression, were transfected with human **bcl-2** gene. Both **bcl-2** and mock transfected COS-1 cells were cultured at low (0.2%) serum concentration for 9 days. The final viable cell number of the **bcl-2** transfected cells was nine-fold of that of the mock transfectants. Both **bcl-2** and mock transfectants were further transfected with the vector pcDNA-lambda containing SV40 ori and immunoglobulin lambda gene for transiently expressing lambda protein. The **bcl-2** expressing COS-1 cells produced more lambda protein than the mock transfected COS-1 cells after 4 days posttransfection. Mouse myeloma p3-X63-Ag.8.653 cells, which are widely used as the partner for preparing hybridoma, and hybridoma 2E3 cells were transfected with human **bcl-2** gene. Both **bcl-2** transfected myeloma and hybridoma survived longer than the corresponding original cells in batch culture. The **bcl-2** transfected 2E3 cells survived 2 to 4 four days longer in culture, producing 1.5- to 4-fold amount of antibody in comparison with the mock transfectants. Coexpression of bag-1 with **bcl-2** improved survival of hybridoma 2E3 cells more than **bcl-2** expression alone. The bag-1 and **bcl-2** coexpressing cells produced more IgG than the cells expressing **bcl-2** alone. Apoptosis of Friend murine erythroleukemia(F-MEL) cells was suppressed with **antisense** c-jun expression. The **antisense** c-jun expressing cells survived 16 days at non-growth state.

1997

3/3,AB/185 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10899777 BIOSIS NO.: 199799520922
Effect of **antisense** oligodeoxynucleotide targeted against **bcl-2** gene on growth and apoptotic susceptibility of leukemia cells.
AUTHOR: Chen Xie-Qun Huang Gao-Sheng; Yang Ping-Di
AUTHOR ADDRESS: Dep. Hematol., Xijing Hosp., Fourth Military Med. Univ., Xi'an 710032**China
JOURNAL: Zhongguo Zhongliu Linchuang 24 (1):p9-12 **1997**
ISSN: 1000-8179
RECORD TYPE: Abstract
LANGUAGE: Chinese; Non-English
SUMMARY LANGUAGE: Chinese; English

ABSTRACT: After treated with **antisense** oligodeoxynucleotide specific for **bcl-2** gene for 3 days, the intrinsic **bcl-2** protein of T-lymphocytic leukemia cell line CEM reduced approximately by 50%, which caused target cells to decrease in survival and to be more sensitive to etoposide-induced apoptosis. The data presented here indicates that cellular intrinsic **bcl-2** protein may play an important role in the leukemic cells death triggered by apoptosis induced chemotherapeutic agents.
1997

3/3,AB/186 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10871162 BIOSIS NO.: 199799492307
Anti-**bcl-2** **ribozyme** sensitizes hormone resistant prostate cancer cells to other therapeutic agents.
AUTHOR: Goluboff Erik T; Dorai Thambi; Olsson Carl A; Katz Aaron E; Buttyan Ralph

AUTHOR ADDRESS: New Yor[redacted]NY**USA
JOURNAL: Journal of Urol[redacted] 157 (4 SUPPL.):p6 **1997**
CONFERENCE/MEETING: 92nd Annual Meeting of the American Urological Association New Orleans, Louisiana, USA April 12-17, 1997
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1997

3/3,AB/187 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10815309 BIOSIS NO.: 199799436454
Determination of **BCL-2 antisense** oligo uptake in peripheral blood stem cell harvests in acute myeloid leukaemia (AML).
AUTHOR: Cunningham A J; Dellow R A; McKelvie N D; Rogers S Y; Craig J I O; Parker A C; Anthony R S
AUTHOR ADDRESS: Dep. Haematology, Edinburgh Royal Infirmary, Edinburgh**UK
JOURNAL: Biochemical Society Transactions 24 (4):p615S **1996**
CONFERENCE/MEETING: 4th International Union of Biochemistry and Molecular Biology Conference Edinburgh, Scotland, UK July 14-17, 1996
ISSN: 0300-5127
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/188 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10770481 BIOSIS NO.: 199799391626
Bcl-1 and **bcl-2** targeting by hammerhead **ribozymes**.
AUTHOR: Pott C(a); Bertram J; Hiddemann W; Kneba M
AUTHOR ADDRESS: (a)Dep. Hematol./Oncol., Univ. Clinics Goettingen, Goettingen**Germany
JOURNAL: Annals of Hematology 73 (SUPPL. 2):pA94 **1996**
CONFERENCE/MEETING: Annual Congress of the German and the Austrian Society of Hematology and Oncology Duesseldorf, Germany October 3-7, 1996
ISSN: 0939-5555
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/189 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10770360 BIOSIS NO.: 199799391505
Design and comparison of **ribozymes** overcoming drug resistance.
AUTHOR: Bertram J; Palfner K; Bruhn T; Stadler H; Hiddemann W; Kneba M
AUTHOR ADDRESS: Dep. Hematol./Oncol., Univ. Clinics Goettingen, Goettingen **Germany
JOURNAL: Annals of Hematology 73 (SUPPL. 2):pA64 **1996**
CONFERENCE/MEETING: Annual Congress of the German and the Austrian Society of Hematology and Oncology Duesseldorf, Germany October 3-7, 1996
ISSN: 0939-5555
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/190 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10760888 BIOSIS NO.: 199799382033
Synthetic **antisense** oligonucleotides: Principles and antileukemic activity.
AUTHOR: Morelli S; Quattrone A; Schiavone N; Calastretti A; Bevilacqua A; Tomasini S; Nicolin A(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol. Univ. Milan, 20129 Milan**Italy
JOURNAL: Oncology Reports 4 (1 SUPPL.):p219-225 **1997**
ISSN: 1021-335X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Inhibition of gene expression by **antisense** oligonucleotides relies on the ability of an ODN to bind a complementary messenger RNA sequence and prevent translation of the mRNA. Most human follicular B cell lymphomas are associated with t(14;18) chromosome translocation that joins the **bcl-2** gene with the IgH locus. This hybrid gene causes upregulation of the **BCL-2** protein expression, endowing cells with survival advantage. The capacity of oligonucleotides to modulate gene expression specifically has been exploited to down regulate the overexpression of **BCL-2** protein in the SU-DHL-4 human follicular B cell lymphoma line by targeting the hybrid transcript with ODN encompassing the unique nucleotide sequence in the fusion region.

1997

3/3,AB/191 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732471 BIOSIS NO.: 199799353616
Response of **bcl-2** expressing cell lines to **antisense** oligonucleotides correlates better with bax.
AUTHOR: Tormo M(a); Tari A; McDonnell T J; Cabanillas F; Garcia-Conde J; Lopez-Berestein G
AUTHOR ADDRESS: (a)Univ. Texas M.D. Anderson Cancer Cent., Houston, TX**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p359A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/192 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10707340 BIOSIS NO.: 199799328485
Arsenic-induced neural tube defects in mice: Alterations in cell cycle gene expression.
AUTHOR: Wlodarczyk Bogdan J; Bennett Gregory D; Calvin Jim A; Finnell Richard H(a)
AUTHOR ADDRESS: (a)Dep. Veterinary Anat. Public Health, Texas A and Univ., College Station, TX 77843-4458**USA
JOURNAL: Reproductive Toxicology 10 (6):p447-454 **1996**
ISSN: 0890-6238
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The potential [redacted] arsenic to cause neural tube d[redacted]cts (NTD) in the human population r[redacted]ins a topic of controversy. Wh[redacted] clearly toxic, the lack of well-defined human epidemiologic studies on this subject has made it difficult to fully understand the effects arsenic may have on the developing human neural tube. In the absence of good clinical data, we have tried to develop a murine model where hypotheses about the reproductive toxicity of arsenate can be tested. For these studies a murine strain (LN/Bc) that has proven to be susceptible to arsenic-induced NTD was use. Because cellular proliferation is vital for normal neural tube closure (NTC) to occur, in the present study we investigated whether an acute arsenate treatment could alter the expression of several cell cycle genes during murine neurulation. Pregnant LM/Bc dams were injected intraperitoneally on gestation day (GD) 7:12 (day:hour) and 8:12 with 40 mg/kg of arsenate, a treatment that causes exencephaly in 90 to 100% of the exposed fetuses. Neural tubes were then isolated from both control and arsenic treated embryos at GD 9:00, 9:12, 10:00, and 10:12, which encompasses all the stages of neurulation for this murine strain. Using the molecular techniques of in situ transcription and **antisense** RNA amplification (RT/aRNA) the expression pattern for **bcl-2**, p53, wee-1, and wnt-1 was analyzed at each of these time points. In the neural tubes isolated from control embryos, the expression of all four genes was significantly altered as neurulation progressed, demonstrating their developmental regulation. Following arsenate treatment, however, there was a significant upregulation in the expression of **bcl-2** and p53 at gestational day 9:0, compared to their control values. The heightened expression of both of these genes suggests that arsenic inhibits cell proliferation, rather than inducing apoptosis, which delayed NTC and ultimately led to the neural tube defects observed in exposed embryos.

1996

3/3,AB/193 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10589729 BIOSIS NO.: 199699210874
Inhibition of **BCL-2** transcription with **antisense** oligonucleotides potentiates MPP+ induced apoptosis.
AUTHOR: Fall C P(a); Bennett J P
AUTHOR ADDRESS: (a)Dep. Neurol., Univ. Virginia Sch. Med., Charlottesville, VA 22908**USA
JOURNAL: Society for Neuroscience Abstracts 22 (1-3):p571 **1996**
CONFERENCE/MEETING: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/194 (Item 41 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10557002 BIOSIS NO.: 199699178147
Gene therapy **antisense** strategy.
AUTHOR: Cotter Finbarr E
AUTHOR ADDRESS: Molecular Haematol. Unit, Inst. Child Health, 30 Guilford St., London WC1N 1EH**UK
JOURNAL: British Journal of Cancer 74 (SUPPL. 28):p7 **1996**
CONFERENCE/MEETING: Joint Meeting of the British Oncological Association, Royal College of Radiologists, British Institute of Radiology and the British Society for Cell Biology Cardiff, Wales, UK July 7-9, 1996

ISSN: 0007-0920
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/195 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10552443 BIOSIS NO.: 199699173588
Ribozymes and cell-permeable peptides allow for transient targeted repression of expression and function of chemoresistance genes and their products.
AUTHOR: Herrmann F; Licht T; Brach M A; Klehntopf M
AUTHOR ADDRESS: Dep. Internal Med. III, Univ. Ulm, Ulm**Germany
JOURNAL: Experimental Hematology (Charlottesville) 24 (9):p1156 **1996**
CONFERENCE/MEETING: 25th Annual Meeting of the International Society for Experimental Hematology New York, New York, USA August 23-27, 1996
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/196 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10551915 BIOSIS NO.: 199699173060
Uptake of **antisense** oligomer to **BCL-2** in bone marrow and peripheral blood stem cell harvests in AML.
AUTHOR: Cunningham A J(a); Dellow R A; Rogers S Y; Craig J I O; Parker A C; Anthony R S
AUTHOR ADDRESS: (a)Dep. Haematol., Edinburghh Royal Infirmary, Scotland**UK
JOURNAL: Experimental Hematology (Charlottesville) 24 (9):p1059 **1996**
CONFERENCE/MEETING: 25th Annual Meeting of the International Society for Experimental Hematology New York, New York, USA August 23-27, 1996
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/197 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10507192 BIOSIS NO.: 199699128337
Inhibition of **BCL-2** by **antisense** oligonucleotides reduces tumor size and reduces chemoresistance of human melanoma in SCID mice.
AUTHOR: Jansen B(a); Wadl H(a); Inoue S A(a); Brown B; Bryan B; Eichler H-G (a); Wolff K; Pehamberger H
AUTHOR ADDRESS: (a)Dep. Clin. Pharmacol., Univ. Vienna, Vienna**Austria
JOURNAL: European Journal of Cancer 32A (SUPPL. 1):pS35 **1996**
CONFERENCE/MEETING: Second Educational Convention of the European School of Oncology Vienna, Austria June 27-29, 1996
ISSN: 0959-8049
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/198 (Item 45 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10449160 BIOSIS NO.: 199699070305
Inhibition of **bcl-2** protein expression by **antisense** S-oligodeoxynucleotides treatment exacerbates neuronal death after cerebral ischemia in rats.
AUTHOR: Chen J; Zhu R; Basta K; Simon R P; Graham S H
AUTHOR ADDRESS: Pittsburgh, PA**USA
JOURNAL: Neurology 46 (2 SUPPL.):pA270-A271 **1996**
CONFERENCE/MEETING: 48th Annual Meeting of the American Academy of Neurology San Francisco, California, USA March 23-30, 1996
ISSN: 0028-3878
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/199 (Item 46 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10409214 BIOSIS NO.: 199699030359
The architecture of mRNA for human **Bcl-2** and its influence on amplification efficiency of RT-PCR.
AUTHOR: Courtright M L; Leaberi R J Ii; Leung M F K L; Leung W-C
AUTHOR ADDRESS: Tulane Univ. Sch. Med., New Orleans, LA 70112**USA
JOURNAL: FASEB Journal 10 (6):pA1092 **1996**
CONFERENCE/MEETING: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/200 (Item 47 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10396603 BIOSIS NO.: 199699017748
Cleavage of the mRNA for the proto-oncogene **BCL-2** by a hammerhead **ribozyme**.
AUTHOR: Dorai Thambi; Olsson Carl A; Buttyan Ralph
AUTHOR ADDRESS: New York, NY**USA
JOURNAL: Journal of Urology 155 (5 SUPPL.):p339A **1996**
CONFERENCE/MEETING: Ninety-first Annual Meeting of the American Urology Association Orlando, Florida, USA May 4-9, 1996
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/201 (Item 48 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10372653 BIOSIS NO.: 199698827571
Screening studies on expression of oncogenes in SRS lymphoma cell lines.
AUTHOR: Zheng Songguo Yin Lianhua(a); Xu Liangzhong(a); Ye Ming; Lu Biao; Zhu Zhendong(a)
AUTHOR ADDRESS: (a)Lab. Pathology, Cancer Hosp., Sch. Basic Med. Sci., Shanghai Med. Univ., Shanghai 200032**China

JOURNAL: Acta Academiae Medicinae Shanghai 23 (1):p7-9 **1996**
ISSN: 0257-8131
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Chinese; Non-English
SUMMARY LANGUAGE: Chinese; English

ABSTRACT: PURPOSE: The studies of oncogenes expression in a SRS - 82 mouse Lymphoma cell line and SAC - II B-2, SAC - II C-3 clones have been less reported. We must establish a oncogene spectrum for finishing the experimental **antisense** treatment to SRS lymphoma. METHODS: SRS - 82 mouse lymphoma cell line and SAC - II B-2, SAC - II C-3 clones were obtained from the Department of Pathophysiology, Shanghai Medical University. ABC immunohistochemical method was used. RESULTS: Strong staining was found for c - fos and c - myc, medium staining for c - jun, ras - p21 and c - erbB - 2, and negative reactions for P53 and **bcl - 2** in SRS - 82 cell line and its clones. Cell surface marks (CD-4 and CD-8) of these two clones and their parent cell line were negative, all of them belong to primary stem cell origin. CONCLUSIONS: Establishments of oncogene spectrum play an important role in the experimental **antisense** treatment in SRS lymphoma, and c - fos and c - myc were the best targets for the **antisense** treatment.

1996

3/3,AB/202 (Item 49 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10358114 BIOSIS NO.: 199698813032
Preclinical pharmacokinetics of G3139, a phosphorothioate **antisense** to **bcl-2** in mice.
AUTHOR: Raynaud F(a); Orr R(a); Goddard P; Dizik M; Beck T; Vaghefi M; Woodle M; Judson I(a); Cotter F
AUTHOR ADDRESS: (a)CRC Cent. Therapeutics, The Inst. Cancer Res., 15 Cotswold Road, Sutton, Surrey**UK
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p411 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/203 (Item 50 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10357662 BIOSIS NO.: 199698812580
Gene therapy of advanced prostate cancer by in vivo transduction with prostate-targeted **antisense** c-myc RNA retroviruses.
AUTHOR: Steiner M S; Anthony C T(a); Lu Y(a); Smithr J A Jr(a); Moses H L (a); Holt J T
AUTHOR ADDRESS: (a)Vanderbilt Univ. Med. Ctr., Nashville, TN 37232**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p344 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/204 (Item 51 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10356506 BIOSIS NO.: 199698811424
Antitumor activity of liposomal-**bcl-2-antisense** oligonucleotides in follicular lymphoma.
AUTHOR: Tormo M(a); Tari A; McDonnell T J; Khodadadlan M; Cabanillas F; Garcia-Conde J; Lopez-Berestein G
AUTHOR ADDRESS: (a)Univ. Texas M. D. Anderson Cancer Center, Houston, TX** USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p173 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

3/3,AB/205 (Item 52 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10291096 BIOSIS NO.: 199698746014
Analysis of apoptosis-related gene expression during the apoptosis of a murine leukemia cell line induced by recombinant human granulocyte-colony stimulating factor (rhG-CSF).
AUTHOR: Kashimura Takuya
AUTHOR ADDRESS: First Dep. Intern. Med., Saitama Med. Sch., Moroyama, Iruma-gun, Saitama 350-04**Japan
JOURNAL: Journal of Saitama Medical School 23 (1):p87-95 **1996**
ISSN: 0385-5074
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Japanese; Non-English
SUMMARY LANGUAGE: Japanese; English

ABSTRACT: In order to investigate the expression of genes related to the apoptosis of leukemic cells, we analyzed apoptosis-related gene expression during the apoptosis of a murine leukemia cell line (C2M-A5) induced by recombinant human granulocyte-colony stimulating factor (rhG-CSF). In the in vitro study using C2M-A5 cells, we found that apoptosis of C2M-A5 cells was induced 48 hours after the addition of rhG-CSF to the culture medium. Northern blot analysis of mRNA derived from C2M-A5 cells revealed overexpression of c-myc (3-24 hours later), H-ras (6 hours later), c-fos (12 hours later), and p53 (6-24 hours later), and down-expression of **bcl-2** (beginning 6 hours later) in the cells cultured with rhG-CSF. However, no change in Fas mRNA expression was observed. The addition of c-myc **antisense** oligonucleotide to the culture of C2M-A5 cells with rhG-CSF significantly inhibited both the growth of clonal cells and the induction of apoptosis of C2M-A5 cells. Flow-cytometry analysis showed a decrease in **Bcl-2** protein in C2M-A5 cells. Based on these findings, we concluded that the apoptosis of.C2M-A5 cells induced by rhG-CSF is associated with changes in expression of c-myc, H-ras, c-fos, p53, and **bcl-2**.

1996

3/3,AB/206 (Item 53 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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10162265 BIOSIS NO.: 199698617183
Resistance of multiple myeloma cells to glucocorticoid-induced apoptosis is restored by cell-permeable peptides targeting functional domains of **BCL-2**.
AUTHOR: Kiehntopf M(a); Herrmann F; Brach M A
AUTHOR ADDRESS: (a)Abt. Medizin. Onkol. Angewandte Molekularbiol., Medizin. Fak., Humboldt-Univ. zu Berlin, Berlin**Germany
JOURNAL: Onkologie 18 (SUPPL. 2):p65 **1995**
CONFERENCE/MEETING: Annual Congress of the German and Austrian Societies for Hematology and Oncology Hamburg, Germany October 8-11, 1995
ISSN: 0378-584X
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/207 (Item 54 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10110203 BIOSIS NO.: 199698565121
Direct evidence for the participation of **bcl-2** in the regulation by retinoic acid of the ara-c sensitivity of leukemic stem cells.
AUTHOR: Hu Z-B; Minden M D; McCulloch E A(a)
AUTHOR ADDRESS: (a)Ontario Cancer Inst., 500 Sherbourne St. Toronto, ON M4X 1K9**Canada
JOURNAL: Leukemia (Basingstoke) 9 (10):p1667-1673 **1995**
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: All-trans retinoic acid (ATRA) increases the sensitivity of AML blast cells to cytosine arabinoside (Ara-C) or daunorubicin (DNR) when ATRA is given after drug. We have proposed that down-regulation of **bcl-2** is part of the mechanism by which ATRA regulates drug sensitivity. To test this hypothesis cDNA encoding **bcl-2** was transfected into cells of the continuous lines OCI/AML-2 and OCI/AML-5. Four transfectant lines were isolated; three contained transfected **bcl-2** in the sense orientation (AML5-BCL2sa, AML5-BCL2sb and 2-bcl2) and one with anti-sense **bcl-2**(AML5-bcl2as). The presence of the transfected gene was demonstrated by Northern blot; translation of the sense transfected genes into protein was demonstrated by Western blotting. Lines with sense-oriented transfected **bcl-2** were significantly less sensitive to Ara-C or H-2O-2 than the parental lines; the cells with anti-sense transfected genes were more sensitive than their parent but the difference did not reach statistical significance. The effect of ATRA on **bcl-2** expression was compared in sense-transfected cells and their parents; by Northern blotting it was shown that the endogenous but not the transfected genes were down-regulated after ATRA exposure. The capacity of cells with transfected genes to respond to ATRA was tested by obtaining Ara-C survival curves for ATRA-treated cells. Compared to controls not exposed to ATRA, the transfected cells showed little or statistically insignificant changes in Ara-C sensitivity after ATRA treatment. We conclude that data from the transfectants provides evidence that expression of **bcl-2** is a determinant of sensitivity to Ara-C and H-2O-2; and that the effect of ATRA on sensitivity requires the presence of **bcl-2** genes in association with regulatory elements.

1995

3/3,AB/208 (Item 55 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10064224 BIOSIS NO.: 199598519142
Induction of bcl-x by CD40 engagement rescues slg-induced apoptosis in murine B cells.
AUTHOR: Wang Zihua; Karras James G; Howard Robert G; Rothstein Thomas L(a)
AUTHOR ADDRESS: (a)Room E-556, Boston Univ. Med. Cent. Hosp., 88 East Newton St., Boston, MA 02118**USA
JOURNAL: Journal of Immunology 155 (8):p3722-3725 **1995**
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD40L, a membrane protein of activated T cells, interacts with the B cell receptor CD40. This interaction has been implicated in the rescue of germinal center B cells from apoptosis and in the rescue of WEHI-231 B lymphoma cells from slg-induced apoptosis. In this report, we have demonstrated that the signal mediated by CD40L acts upon bcl-x, a **bcl-2** homologue. bcl-x expression is strongly enhanced by CD40 receptor engagement, while there is little or no induction by slg cross-linking. The expression of bax and **bcl-2** is not significantly affected by either CD40L or slg crosslinking. **Antisense** but not sense phosphorothioate oligonucleotide for, bcl-x can partially block this CD40-mediated apoptotic rescue. This result suggests that the up-regulation of bcl-x by CD40L plays an important role in CD40-mediated apoptotic rescue in murine B cells.

1995

3/3,AB/209 (Item 56 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10029761 BIOSIS NO.: 199598484679
Glucocorticoid-induced programmed-cell death (apoptosis) is inhibited in transgenic mice expressing type II glucocorticoid receptor (GR) **antisense** RNA: Down-regulation of **Bcl-2** and interleukin 2 (IL-2R) receptor overexpression.
AUTHOR: Morale M C(a); Bartoloni G; Italia F; Gallo F; Barden N; Marchetti B
AUTHOR ADDRESS: (a)Dep. Pharm., Catania**Italy
JOURNAL: Society for Neuroscience Abstracts 21 (1-3):p1395 **1995**
CONFERENCE/MEETING: 25th Annual Meeting of the Society for Neuroscience San Diego, California, USA November 11-16, 1995
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/210 (Item 57 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09983852 BIOSIS NO.: 199598438770
Cell-permeable peptides covering the NIP-recognition site of **BCL-2** and **BCL-2** specific hammerhead **ribozymes** restore sensitivity of multiple myeloma cells to glucocorticoid-induced

apoptosis.
AUTHOR: Kiehntopf M; Her[redacted]n F; Brach M A
AUTHOR ADDRESS: Abt. fuer Med. Onkol. Angewandte Molekular Biol., Med. Fakultaet Humboldt-Univ., Berlin**Germany
JOURNAL: Experimental Hematology (Charlottesville) 23 (8):p905 **1995**
CONFERENCE/MEETING: 24th Annual Meeting of the International Society for Experimental Hematology Duesseldorf, Germany August 27-31, 1995
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/211 (Item 58 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09983796 BIOSIS NO.: 199598438714
C-MYC **antisense** transcripts accelerate differentiation and start apoptosis in human leukemia cells.
AUTHOR: Hao X J; Tang P H; Du D L; Mao M; Wu M
AUTHOR ADDRESS: Sinochem Inst. Biotechnol., Inst. Basic Med. Sci., Beijing **China
JOURNAL: Experimental Hematology (Charlottesville) 23 (8):p888 **1995**
CONFERENCE/MEETING: 24th Annual Meeting of the International Society for Experimental Hematology Duesseldorf, Germany August 27-31, 1995
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/212 (Item 59 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09758216 BIOSIS NO.: 199598213134
Antisense oligonucleotide induced growth factor deprivation in PC-3 cells enhances **BCL-2** expression.
AUTHOR: Rubenstein Marvin; Mirochnik Yelena; McKiel Charles F; Guinan Patrick
AUTHOR ADDRESS: Chicago, IL**USA
JOURNAL: Journal of Urology 153 (4 SUPPL.):p270A **1995**
CONFERENCE/MEETING: Ninetieth Annual Meeting of the American Urological Association Las Vegas, Nevada, USA April 23-28, 1995
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/213 (Item 60 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09749143 BIOSIS NO.: 199598204061
Comparison of the effects on K 562 cells of **ribozymes** targeted against BCR/ABL and **BCL-2** mRNAs.
AUTHOR: Lange W; Daskalakis M; Scheid S; Doelken G; Finke J
AUTHOR ADDRESS: Abt. Haematologie Onkologie, Med. Univ.-Klinik Freiburg, Hugstetter Str. 55, D-79106 Freiburg**Germany
JOURNAL: Journal of Cellular Biochemistry Supplement 0 (19A):p222 **1995**
CONFERENCE/MEETING: Keystone Symposium on Ribozymes: Basic Science and Therapeutic Applications Breckenridge, Colorado, USA January 15-21, 1995

ISSN: 0733-1959
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/214 (Item 61 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09746901 BIOSIS NO.: 199598201819
Antisense p53 inhibits apoptosis in myeloma cells through **bcl-2** overexpression.
AUTHOR: Iyer R(a); Ding L; Saylors R; Srivastava A; Barlogie B; Munshi N
AUTHOR ADDRESS: (a)Univ. Arkansas Med. Sci., John McClellan VA Med. Cent., Little Rock, AR**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 36 (0):p560 **1995**
CONFERENCE/MEETING: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/215 (Item 62 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09746006 BIOSIS NO.: 199598200924
Deregulation of **BCL-2** expression in t(14;18) cells by an **antisense** transcript.
AUTHOR: Morelli S(a); Capaccioli S; Quattrone A; Schiavone N; Calastretti A (a); Copreni E(a); Canti G(a); Gong L(a); Nicolin A(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Univ. Milan, Milan**Italy
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 36 (0):p409 **1995**
CONFERENCE/MEETING: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1995

3/3,AB/216 (Item 63 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09616275 BIOSIS NO.: 199598071193
In vivo engraftment and **BCL-2 antisense** treatment of low grade B-cell lymphoma lymph node biopsies in SCID mice.
AUTHOR: Cotter F; Hill M; Pocock C; Clarke P; Malone M; Cunningham D
AUTHOR ADDRESS: Dep. Haematol., Inst. Child Health, 30 Guilford St., London WC1 N1EH**UK
JOURNAL: Blood 84 (10 SUPPL. 1):p640A **1994**
CONFERENCE/MEETING: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/217 (Item 64 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09615212 BIOSIS NO.: 199598070130
Effectiveness of **BCL-2 antisense** oligodeoxynucleotides (AS-ODN) against human follicular small-cleaved cell lymphoma (FSCCL)-SCID mice xenograft model.
AUTHOR: Abubakr Y A(a); Mohammad R; Maki A; Dan M; Du W; Smith M R; Al-Katib A
AUTHOR ADDRESS: (a)Div. Hematol./Oncol., Wayne State Univ., Detroit, MI** USA
JOURNAL: Blood 84 (10 SUPPL. 1):p374A **1994**
CONFERENCE/MEETING: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/218 (Item 65 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09614944 BIOSIS NO.: 199598069862
Expression, in vivo modelling, and molecular modification of survival genes in T(4;11) associated infant leukemias.
AUTHOR: Pocock C F E(a); Evans M; Booth M(a); Malone M; Greil J; Morgan G (a); Cotter F F(a)
AUTHOR ADDRESS: (a)Dep. Haematol. Oncol., Inst. Child Health, London WC1N 1EH**UK
JOURNAL: Blood 84 (10 SUPPL. 1):p307A **1994**
CONFERENCE/MEETING: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/219 (Item 66 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09614286 BIOSIS NO.: 199598069204
Inhibition of **BCL-2** with **antisense** oligo-nucleotides induces apoptosis and increases the sensitivity of AML blasts to cytosine arabinoside.
AUTHOR: Keith F J; Bradbury D A; Zhu Y M; Russell N H
AUTHOR ADDRESS: Russell Dep. Haematol., Nottingham City Hosp., Nottingham **UK
JOURNAL: Blood 84 (10 SUPPL. 1):p142A **1994**
CONFERENCE/MEETING: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/220 (Item 67 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09473053 BIOSIS NO.: 199497481423
Antisense oligonucleotides directed to the initiation codon of **BCL-2** interfere with PRO-B cell proliferation.
AUTHOR: Gibson L F(a); Narayanan R; Piktel D; Landreth K S
AUTHOR ADDRESS: (a)Dep. Pediatr., West Va. Univ. Health Sci. Cent., Morgantown, WV 26506**USA
JOURNAL: Experimental Hematology (Charlottesville) 22 (8):p732 **1994**
CONFERENCE/MEETING: 23rd Annual Meeting of the International Society for Experimental Hematology Minneapolis, Minnesota, USA August 21-25, 1994
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/221 (Item 68 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09381887 BIOSIS NO.: 199497390257
In vivo suppression of lymphoma with **BCL-2 antisense** oligonucleotides.
AUTHOR: Pocock C(a); Al-Mahdi N; Hall P; Morgan G; Cotter F(a)
AUTHOR ADDRESS: (a)LRF Dep. Haematology Oncology, Inst. Child Health, 30 Guilford Street, London WC1N 1EH**UK
JOURNAL: British Journal of Haematology 86 (SUPPL. 1):p24 **1994**
CONFERENCE/MEETING: Annual Scientific Meeting of the British Society for Haematology Harrogate, England, UK April 25-28, 1994
ISSN: 0007-1048
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/222 (Item 69 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09294301 BIOSIS NO.: 199497302671
Reduction of chemoresistance and induction of apoptosis by **antisense** downregulation of **bcl-2**.
AUTHOR: Kitada S(a); Takayama S(a); Deriel K; Stein C A; Reed J C(a)
AUTHOR ADDRESS: (a)La Jolla Cancer Res. Found., La Jolla, CA 92037**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 35 (0):p318 **1994**
CONFERENCE/MEETING: 85th Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/223 (Item 70 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09289873 BIOSIS NO.: 199497298243
Growth inhibition of a gastric cancer cell line by **antisense** oligonucleotides to c-myc and **bcl-2**.
AUTHOR: Nagano K; Kawano S; Kobayashi I; Nakama A; Fusamoto H; Kamada T

AUTHOR ADDRESS: First Dep. Med., Osaka Univ. Sch. Med., Osaka**Japan
JOURNAL: Gastroenterology 106 (4 SUPPL.):pA419 **1994**
CONFERENCE/MEETING: 95th Annual Meeting of the American Gastroenterological Association New Orleans, Louisiana, USA May 15-18, 1994
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
1994

3/3,AB/224 (Item 71 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09202765 BIOSIS NO.: 199497211135
Role of the apoptosis-related **BCL-2** gene in hemopoietic tissues and modulation by **antisense** oligonucleotides.
AUTHOR: Aiello A; Delia D; Fontanella E; Pierotti M A
AUTHOR ADDRESS: Oncologia Sperimentale A., Ist. Naz. Tumori, Milano**Italy
JOURNAL: European Journal of Histochemistry 37 (SUPPL. 2):p92 **1993**
CONFERENCE/MEETING: Tenth National Meeting of the Gruppo Italiano di Citometria (Italian Cytometry Group) on The Cell: Structure and Function Orvieto, Italy September 28-October 1, 1993
ISSN: 1121-760X
RECORD TYPE: Citation
LANGUAGE: English
1993

3/3,AB/225 (Item 72 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09098270 BIOSIS NO.: 199497106640
In vivo suppression of B-cell lymphoma with **BCL-2** **antisense** oligonucleotides.
AUTHOR: Pocock C; Al-Mahdi N; Hall P; Morgan G; Cotter F
AUTHOR ADDRESS: Dep. Haematol., Inst. Child Health, 30 Guilford St., London WC1N 1EH**UK
JOURNAL: Blood 82 (10 SUPPL. 1):p200A **1993**
CONFERENCE/MEETING: Thirty-fifth Annual Meeting of the American Society of Hematology St. Louis, Missouri, USA December 3-7, 1993
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1993

3/3,AB/226 (Item 73 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09097947 BIOSIS NO.: 199497106317
BCL-2 antisense oligodeoxynucleotides block in-vitro proliferation and survival of normal marrow progenitors and myeloid leukemia cells.
AUTHOR: Campos L; Guyotat D
AUTHOR ADDRESS: Lab. Hematol., Fac. Med., St. Etienne**France
JOURNAL: Blood 82 (10 SUPPL. 1):p119A **1993**
CONFERENCE/MEETING: Thirty-fifth Annual Meeting of the American Society of Hematology St. Louis, Missouri, USA December 3-7, 1993
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

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  File   5:Biosis Previews(R)  1969-2001/Jul W5
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          29715  ANTISENS?
           5192  RIBOZYM?
       16069992  PY<1993
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...completed examining records
      S2       6  RD (unique items)
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 1/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07844869   92199001   PMID: 1312868
  Antisense inhibition of oncogene expression.
  Neckers L; Whitesell L; Rosolen A; Geselowitz DA
  Clinical  Pharmacology  Branch,  National  Cancer  Institute,  National
Institutes of Health, Bethesda, MD 20892.
  Critical  reviews  in oncogenesis (UNITED STATES)   1992,  3  (1-2)
 p175-231,  ISSN 0893-9675   Journal Code: A1Y
  Languages: ENGLISH
  Document type: Journal Article; Review; Review, Academic
  Record type: Completed
  To  understand  the  role  of  individual  genes in regulating biological
processes,  one  must  be  able to interfere specifically with either their
expression or function. While monoclonal antibodies have proven very useful
in studying cell surface proteins, the specific inhibition of intracellular
proteins  in  viable  cells  is  a much more difficult problem. The goal of
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antisense technology is to develop small oligonucleotides, plasmids, or retroviral vectors which can be readily introduced into living cells in order to inhibit specific gene expression. In this review, we briefly describe the principles of **antisense** usage, including problems of cellular uptake and intracellular distribution, mechanism of **antisense** action, and the properties of various oligonucleotide derivatives. In addition we present several examples of the biological effects of **antisense** administration used to study the role of specific genes in the regulation of cell growth and differentiation.

1/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07833584 91301181 PMID: 2070813
Mitochondrial protein p26 BCL2 reduces growth factor requirements of NIH3T3 fibroblasts.
Reed JC; Talwar HS; Cuddy M; Baffy G; Williamson J; Rapp UR; Fisher GJ
University of Pennsylvania School of Medicine, Department of Pathology and Laboratory Medicine, Philadelphia 19104.
Experimental cell research (UNITED STATES) Aug **1991**, 195 (2) p277-83, ISSN 0014-4827 Journal Code: EPB
Contract/Grant No.: AR39691, AR, NIAMS; CA49576, CA, NCI; FO5DW04545, PHS ; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The BCL2 (B cell lymphoma/leukemia-2) proto-oncogene encodes a 26-kDa protein that has been localized to the inner mitochondrial membrane and that has been shown to enhance the survival of some types of hematopoietic cells. Here we show that NIH3T3 fibroblasts stably transfected with a BCL2 expression plasmid exhibit reduced dependence on competence-inducing growth factors (platelet-derived growth factor, PDGF; epidermal growth factor, EGF) for initiation of DNA synthesis. The importance of BCL2 for growth factor-induced proliferation of these cells was further confirmed by the useage of BCL2 **antisense** oligodeoxynucleotides. The mechanisms by which overexpression of p26 BCL2 contributes to fibroblast proliferation are unknown, but do not involve alterations in: (a) the production of inositol triphosphates (IP3), (b) PDGF-induced transient elevations in cytosolic Ca2+ ions, or (c) the activity of protein kinase C enzymes in these transfected cells. The results imply that changes in mitochondrial functions play an important role in the early stages of the cell cycle that render 3T3 cells competent to respond to the serum progression factors that stimulate entry into S-phase.

1/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07817990 94115767 PMID: 1342969
Analysis of BCL2 and MYC expression in non-Hodgkin's lymphomas by in situ hybridization: correlation with chromosome translocations.
Murty VV; Ladanyi M; Houldsworth J; Mikraki V; Chaganti RS
Laboratory of Cancer Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
Diagnostic molecular pathology (UNITED STATES) Dec **1992**, 1 (4) p221-8, ISSN 1052-9551 Journal Code: BY3
Contract/Grant No.: CA-20194, CA, NCI; CA-34775, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have used an in situ hybridization method for analysis of expression of BCL2 and MYC on cytospun preparations of normal and malignant lymphoid cell lines and tissue sections of normal and malignant lymph nodes. The probes comprised 50-mer **antisense** oligonucleotides starting at the

ATG codons of exon 3 of BCL2 and exon 2 of MYC. We studied the expression of these two genes in frozen tissue sections of biopsy specimens derived from normal and hyperplastic lymph nodes, B-cell lymphomas carrying the t(14;18)(q32;q21) and t(8;14)(q24;q32) translocations, and T-cell lymphomas with clonal chromosome abnormalities. While all proliferating cells expressed both genes, BCL2 expression was increased two- to threefold in follicular lymphomas with t(14;18) and MYC expression was increased two- to four-fold in high-grade lymphomas with t(8;14). These results are consistent with previous data on deregulated expression of these genes obtained from study of lymphoma cell lines carrying the relevant translocations.

1/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07735703 91004004 PMID: 2208117
Antisense-mediated inhibition of BCL2 protooncogene expression and leukemic cell growth and survival: comparisons of phosphodiester and phosphorothioate oligodeoxynucleotides.
Reed JC; Stein C; Subasinghe C; Haldar S; Croce CM; Yum S; Cohen J
Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia 19104-6082.
Cancer research (UNITED STATES) Oct 15 **1990**, 50 (20) p6565-70, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA-47946, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Antisense oligodeoxynucleotides specific for sequences in mRNAs from the B-cell lymphoma/leukemia-2 (BCL2) gene were used to inhibit the growth in culture of a human leukemia cell line, 697. Normal phosphodiester (PO) and nuclease-resistant phosphorothioate (PS) oligodeoxynucleotides were compared with regard to specificity, potency, and kinetics. Both PO and PS **antisense** BCL2 oligodeoxynucleotides were specific inhibitors of cellular proliferation, since sense versions of these synthetic DNAs were inactive at similar concentrations. Specificity was further confirmed by quantitative immunofluorescence studies, showing that PO and PS **antisense** BCL2 oligodeoxynucleotides (when used at appropriate concentrations) reduced levels of BCL2 protein without influencing expression of HLA-DR and other control antigens. The onset of inhibition by PO oligodeoxynucleotides was faster, with reductions in cell numbers occurring within 1 day of addition to cultures, in contrast to phosphorothioates, which were ineffective until 3-4 days. Phosphorothioates were more potent that phosphodiesters, however, with half-maximal inhibition of leukemic cell growth occurring at concentrations 5-10 times lower. As expected from previous studies demonstrating the importance of BCL2 for regulating lymphoid cell survival, BCL2 **antisense** oligodeoxynucleotides also led to 697 leukemic cell death through sequence-specific mechanisms, with reductions in cellular viability generally lagging the inhibitory effects on cellular growth by about 2 days. Taken together, these data indicate that PO and PS oligodeoxynucleotides targeted against the human BCL2 protooncogene can be sequence-specific inhibitors of leukemic cell growth and survival.

1/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07726696 93310901 PMID: 1306320
Selective anti-gene therapy for cancer: principles and prospects.
Cohen JS
Cancer Pharmacology Department, Georgetown University Medical School, Rockville, MD.
Tohoku journal of experimental medicine (JAPAN) Oct **1992**, 168

(2) p351-9, ISSN 0040-8727 Journal Code: VTF
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

Oligodeoxynucleotides can act as **antisense** complements to target sense sequences of natural mRNAs to selectively regulate gene expression by translation arrest. This is a form of interventional gene therapy. Chemically modified analogs that are nuclease-resistant enable this strategy to be utilized in practice. Of the chemically modified backbone analogs of oligodeoxynucleotides we have used the phosphorothioate (PS) analog, in which a non-bridging phosphate oxygen atom is substituted with a sulfur atom. We have shown that these oligodeoxynucleotide analogs inhibit beta-globin expression in cell free systems, and that they are taken up by cells. Specific sequences have been shown to selectively regulate viral and cellular gene expression, for example the **bcl-2** oncogene that is found in ca. 90% of lymphomas. However, the PS analog has certain disadvantages, notably reduced hybridization and non-selective inhibition of translation. We have therefore synthesized a series of (PS-PO) co-polymers and characterized their properties. Other related approaches include catalytic **ribozymes** , and formation of triplexes by direct interaction of oligomers in the major groove of DNA. In general, a chemically modified oligodeoxynucleotide analog can be regarded as a novel form of informational drug.

1/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06949787 93136502 PMID: 1369122
Oligonucleotide therapy.
Crooke ST
Isis Pharmaceuticals, Carlsbad, California 92008.
Current opinion in biotechnology (ENGLAND) Dec **1992**, 3 (6) p656-61, ISSN 0958-1669 Journal Code: A92
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

Rapid progress in oligonucleotide therapeutics has continued over the past year as major programs established in the past four years have grown and begun to be productive. Important advances were reported in the medicinal chemistry of oligonucleotides and in understanding their pharmacodynamic properties. Significant progress was made in understanding the pharmacokinetic and toxicologic properties of first generation analogs, particularly phosphorothioates and one oligonucleotide, ISIS 2105, entered clinical trials. Additionally, combinatorial approaches designed to identify oligonucleotides that may bind to a variety of targets were reported.